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AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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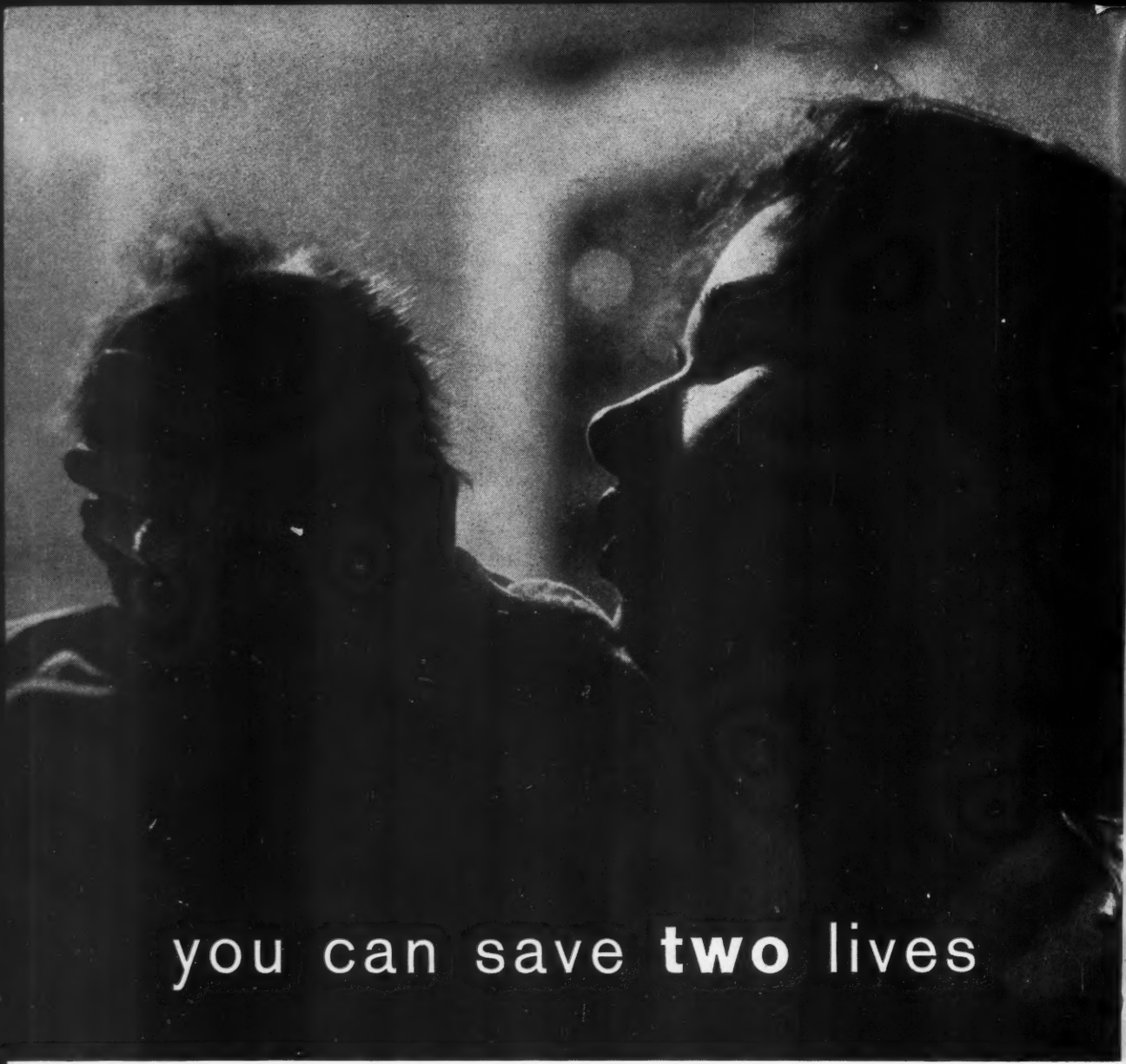
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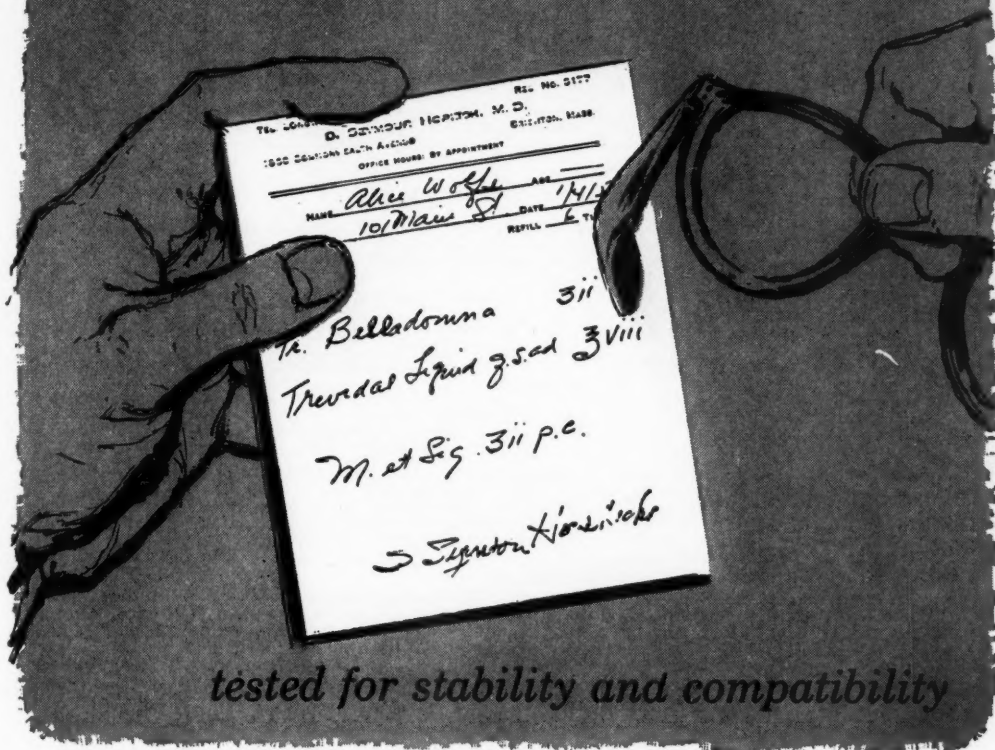
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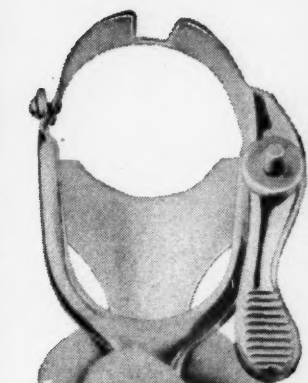
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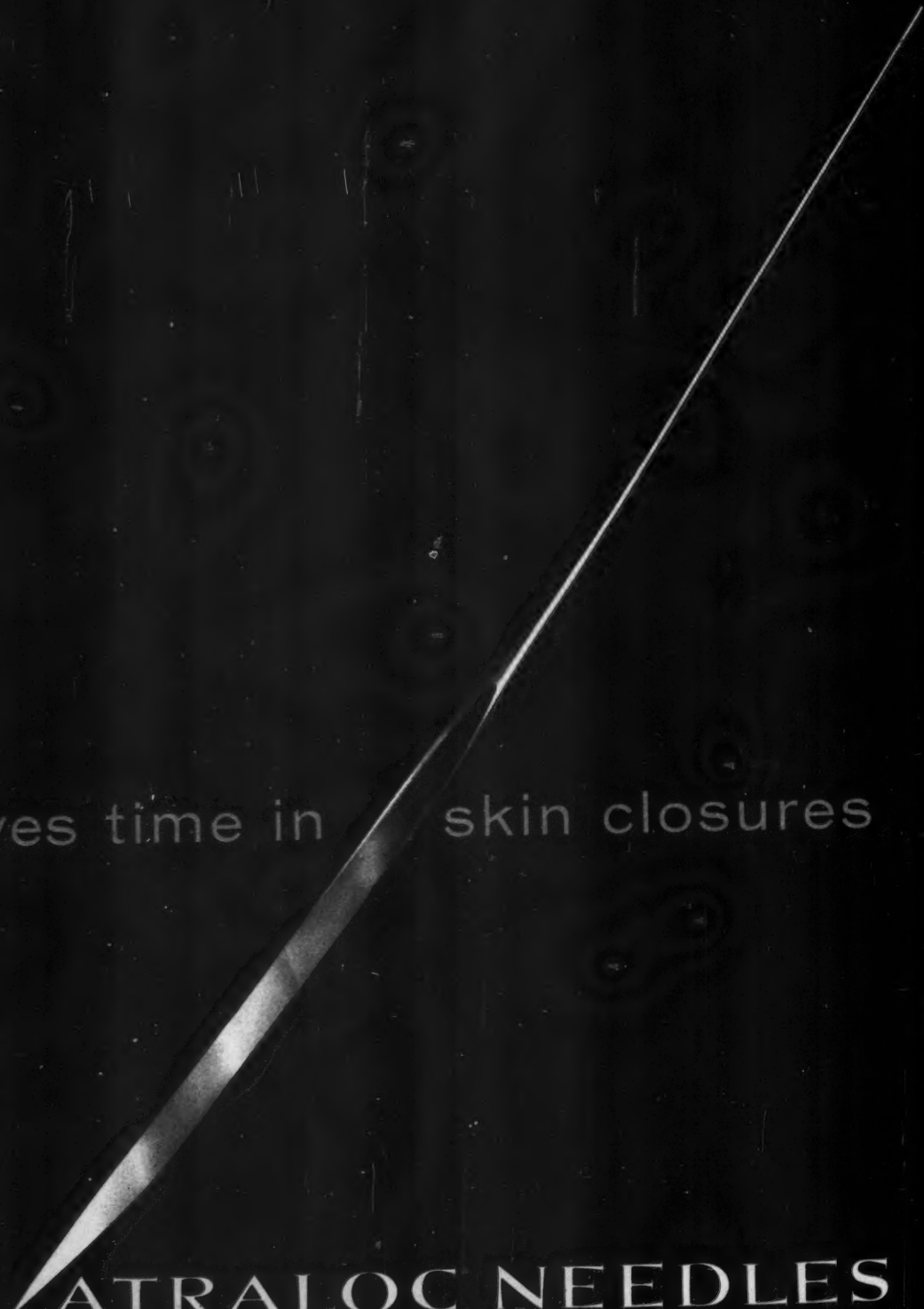
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1. Conner, P. K., Jr., and Moyer, J. H.: *GP* 14:124 (Nov.) 1956.
2. Kinney, J. J.: *J. M. Soc. New Jersey* 53:128 (March) 1956.
3. Weil, L. L.: *Florida J. Gen. Pract.* 4:9 (July) 1954.
4. Report of Study by Army, Navy, Air Force Motion Sickness Team: *J.A.M.A.* 160:755 (March 3) 1956.

^{*}Trademark

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.



June, 1957

Page 9

new extensive studies¹ show at least

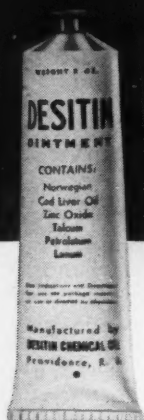
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"over other accepted

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tubes of 1 oz.,
2 oz., 4 oz., and
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1. helps achieve "early, clean and healthy healing".
2. serves to protect the wound from mechanical and chemical injury, and from bacterial contamination.
3. helps check infection.
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1. Grayzel, H. G., and Schapiro, S.: *Western J. Surg., Obstet. & Gynec.*, Oct. 1956.

Am. J. Obst. & Gynec.

in postmenopausal vaginitis
in vaginal plastic surgery

ORTHO®

Dienestrol

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vaginal estrogen therapy

builds vaginal epithelium





NEW

HOW TO COMFORT THE OB PATIENT AND SAVE NURSING TIME

In the past two years, hundreds of hospitals have adopted Americaine Aerosol as the routine spray-on relief for painful post-episiotomies, tender hemorrhoids, and fissured nipples.

Americaine Aerosol is the first aerosol preparation to be provided for this use. It offers the same potent topical agent as Americaine Ointment (20% dissolved benzocaine), and it is quick, easy to apply, and sanitary.

HOW TO GET BEST RESULTS AND ECONOMY IN APPLICATION

Americaine Aerosol is so easy to use, it can be applied by the nurse or by the patient, herself: Hold dispenser 8" to 12" from area and press button to release spray. Spray

sufficient to give good coverage without waste. Do not apply pad or other dressing for about 5 to 10 minutes after application, as this may soak up some of the medication and reduce effect. Do not hold dispenser upside down.

AMERICAINE AEROSOL FEATURES THAT MERIT YOUR ATTENTION

1. Americaine provides relief in 2-3 minutes. Relief usually lasts 4-6 hours.
2. Americaine Aerosol should not be confused with any other aerosols or topical analgesics containing a much lower percentage of active drug. Only Americaine contains 20% dissolved benzocaine for faster, more prolonged relief.
3. Americaine is a simple, uncomplicated formula. This minimizes possibility of sensitivity. Not a single case of sensitivity was reported in over 11,800 published cases. (Reprints on request.)

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**SMALL
SIZE!**

New 3 oz. dispenser is easy for patient to use.

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NOW, THREE SIZES: 11 oz. size for professional use and floor stock, 5.5 oz. and 3 oz. sizes for your prescriptions.

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Even stubborn
trichomoniasis yields...
because Tricofuron
is effective
during menstruation,
the critical time
for therapy.



TRICOFURON®

Recurrences of trichomoniasis "are most likely to follow the menstrual period."¹

"Over and over again today patients are seen with what is said to be an intractable, treatment-resistant *Trichomonas* infestation, but history-taking often reveals that such patients have never had treatment prescribed during any menstrual period."²

Menstrual blood in the vagina "forms an excellent medium for the rapid multiplication of *T. vaginalis*"³ and "lowers the acidity of the vagina and hence there is a tendency to recrudescence [of trichomoniasis] at that time."⁴

Tricofuron is powerfully trichomonacidal "even in the presence of vaginal debris and menstrual blood."³

*For 44 of 48 patients: lasting cure was obtained with a single course of Tricofuron therapy.*³

Vaginal Suppositories—for home use—each morning and night through one cycle, including the important menstrual days. Contain 0.25% Furoxone® (brand of furazolidone) in a water-miscible base. Box of 12, each sealed in green foil.

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References: 1. Bernstine, J. B., and Rakoff, A. E.: *Vaginal Infections, Infestations and Discharges*, New York, The Blakiston Company, Inc., 1953, p. 235. 2. Overstreet, E. W.: *Arizona M.* 10:383, 1953. 3. Schwartz, J.: *Obst. Gyn.*, N. Y. 7:312, 1956. 4. Crossen, R. J.: *Diseases of Women*, St. Louis, The C. V. Mosby Company, 1953, p. 292.

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in ALL pregnancies . . .*

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REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gilman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
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5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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Vitamin A	2000 U.S.P. Units
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Thiamine Mononitrate (B ₁)	2 mg.
Riboflavin (B ₂)	2 mg.
Niacinamide	7 mg.
Vitamin B ₁₂	1 mcgm.
Vitamin K (Menadione)	0.5 mg.
Ascorbic Acid (C)	35 mg.
Folic Acid	1 mg.
Calcium (in CaHPO ₄)	250 mg.
Phosphorus (in CaHPO ₄)	190 mg.
Dicalcium Phosphate Anhydrous (CaHPO ₄)	869 mg.
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Manganese (in MnSO ₄)	0.12 mg.

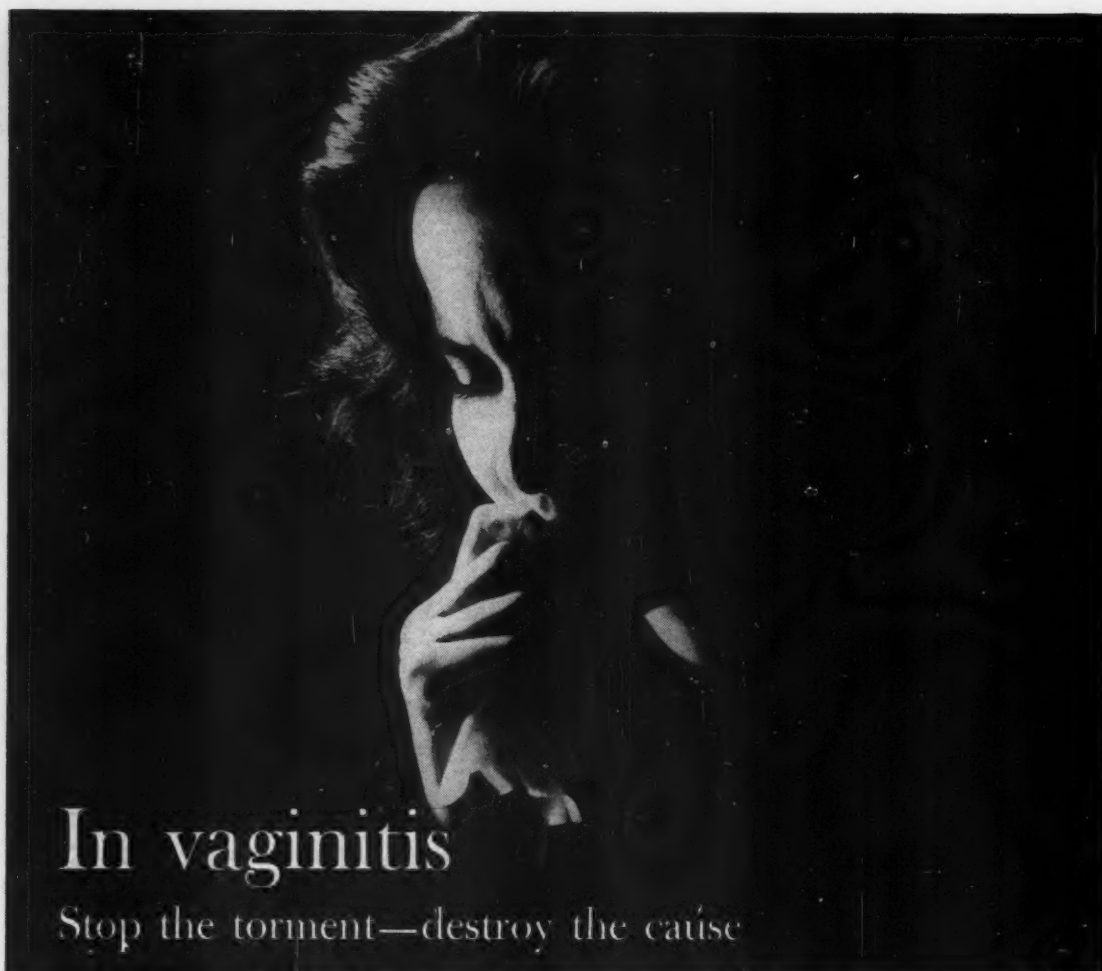
Dosage: 1 to 3 capsules, throughout pregnancy and lactation



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In vaginitis

Stop the torment—destroy the cause

AVC

Improved



in trichomonal vaginitis —
*"... the most effective
 treatment available."¹*



in monilial vaginitis —
*"... more effective than any
 other agent . . . used previously."²*



in mixed infection —
*"... the most effective
 treatment of endocervicitis. . . ."³*

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.¹ Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

Indications: Trichomonal leukorrhea; monilial and nonspecific vaginitis; cervicitis; postpartum hygiene; pre- and postcauterization, coagulation, conization, and other vaginal surgery; vaginal infections in children.

Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. 2:45, 1955. (2) Hensel, H. A.: Postgrad. Med. 8:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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***Times Square's** largest sign isn't big enough to cover all the pages of scientific reports published on GANTRISIN.

The efficacy of GANTRISIN as an anti-bacterial agent is recognized everywhere. Of its ten forms it can be said that each provides an action against infections that is decisive, rapid, enduring and, above all, safe.

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for infections
in children —*



LIPO GANTRISIN

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**provides therapeutic blood levels of time-proved Gantrisin
around-the-clock—with only two doses daily**

DESCRIPTION:

Lipo Gantrisin should be considered for use in many systemic and urinary tract infections because it provides:

1. the time-proved wide-spectrum antibacterial action of Gantrisin in a stable, free-flowing homogenized emulsion
2. convenience of therapeutic blood levels for 24 hours with just two daily doses
3. delicious taste that assures wide acceptance by children and adults
4. no need for forced fluids...no danger of renal blocking or secondary fungus growth

INDICATIONS:

Systemic and urinary tract infections due to streptococci, staphylococci, pneumococci, H. influenzae, K. pneumoniae, meningococci, E. coli, B. proteus, B. pyocyaneus, A. aerogenes, B. paracolon and Alcaligenes fecalis.

DOSAGE:

Children:	teaspoonfuls every 12 hours
20 lbs	1
40 lbs	1½
60 lbs	2
80 lbs	3
Adults:	4

CAUTION:

The usual precautions in sulfonamide therapy should be observed.

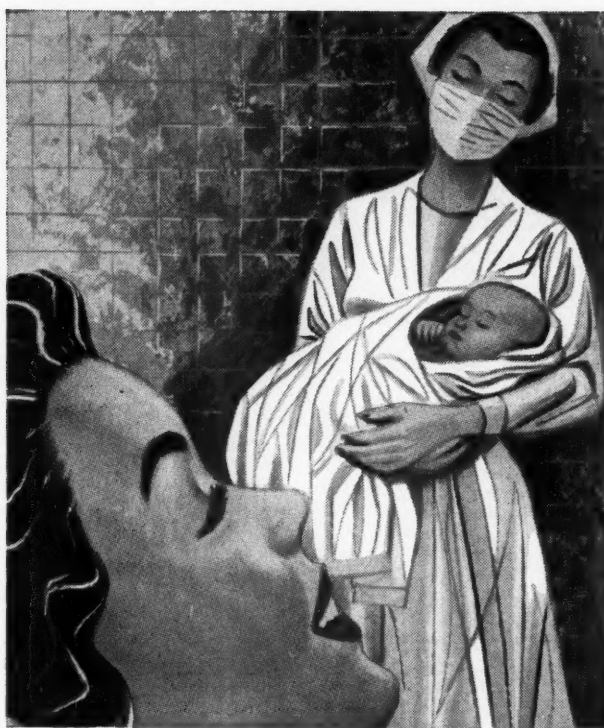
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Lipo Gantrisin Acetyl, containing 20 per cent Gantrisin (1 Gm per 5 cc in the form of Gantrisin Acetyl), in a palatable, readily digestible homogenized emulsion that prolongs the action of the drug. In bottles of 4 and 16 oz.

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Satisfactory results were obtained in over 96 per cent of cases in a series of 267 patients who received estrogen and androgen as combined in "Premarin" with Methyltestosterone. Therapy was started as soon as possible after delivery. No untoward side effects were noted. In addition, the absence of mental depression in the puerperium was considered of notable importance.*

*Fiskio, P. W.: GP 11:70 (May) 1955.

"PREMARIN"® with METHYLTESTOSTERONE

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Sigmamycin*

OLEANDOMYCIN TETRACYCLINE

provides added certainty in antibiotic therapy particularly for that 90% of the patient population treated in home or office...

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Supplied: SIGMAMYCIN CAPSULES — 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.), bottles of 16 and 100; 100 mg. (oleandomycin

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effective vulvovaginal therapy

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a detergent... a bactericide and fungicide...

an antipruritic... an aid to epithelization...

an aesthetic and psychosomatic adjunct

Trichotine douches — incorporating the multiple advantages of sodium lauryl sulfate with the recognized values of other specific or adjunctive agents — may be prescribed as often as required in cases of nonspecific vaginitis and leukorrhea, subacute and chronic cervicitis, senile vaginitis, trichomoniasis, and moniliasis; hot packs are often quickly effective in pruritus vulvae.

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the 24-hour vaginal pH stabilizer

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In your management of constipation

when bowel motility is inadequate, prescribe

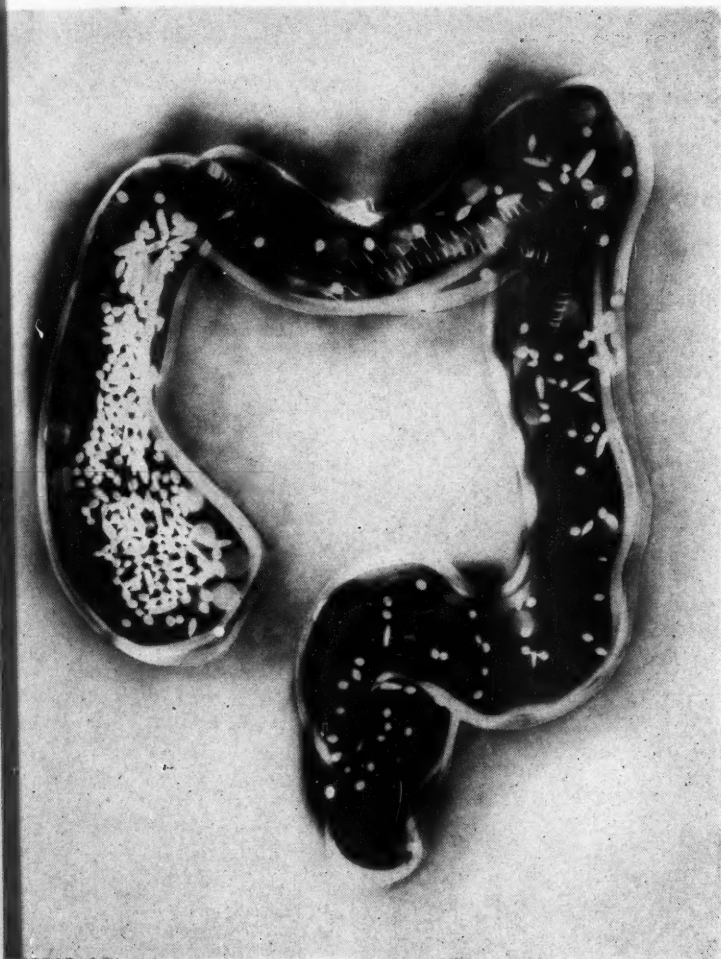
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1. Seegar, J.K.B.E., and Devlin, A.J.: Maryland M.J. 5:330 (June) 1956.

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1. Dieckmann, W. J., and Piddle, H. D.: Anemia of Pregnancy Treated with Molybdenum-Iron Complex, *Am. J. Obst. & Gynec.* 57:541, (March) 1949.
2. Neary, E. R.: *Am. J. Med. Sc.* 212:76 (July) 1946.
3. Kelly, H. T.: *Pennsylvania M. J.* 51:999 (June) 1948.

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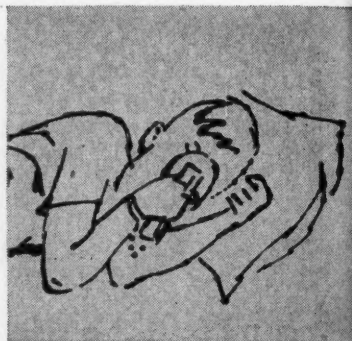
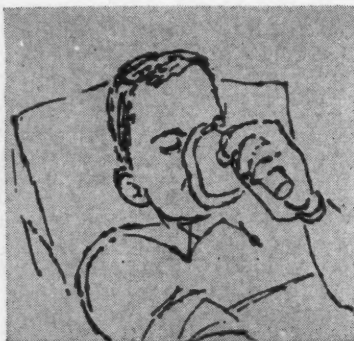
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—Oxygenation in Obstetrics: J. C. Dunlap and W. W. Brown; *Obstetrics & Gynecology*, 3:496, May, 1954.

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Adrenosem Salicylate has been used prophylactically and therapeutically in virtually every operative procedure. Case histories have been published on its successful use in the following procedures and conditions:

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Hemoptysis
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Metrorrhagia and
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1. Bacala, J.C.: The Use of the Systemic Hemostat,
Carbazochrome Salicylate, West. J. Surg. 64:88 (Jan., 1956)

*U.S. Pat. 2581850, 2506294

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A short history-in quotes-of

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Salicylate

"... a potent antihemorrhagic factor."

Sherber, D.A.: The Control of Bleeding, Am. J. Surg. 86:331 (Sept., 1953)

"... since that date (1953) Adrenosem has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagologic procedures..."

Peele, J.C.: Adrenosem in the Control of Hemorrhage from the Nose and Throat, A.M.A. Arch. of Otolaryng. 61:450 (April, 1955)

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Bacala, J.C.: The Use of the Systemic Hemostat Carbazochrome Salicylate, West. J. Surg. 64:88 (Jan., 1956)

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Owings, Capers B.: The Control of Postoperative Bleeding with Adrenosem, Laryngoscope 55:21 (Jan., 1955)

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Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N.Y. State J. Med. 55:886 (Mar., 1956)

"Adrenosem Salicylate is nontoxic and has a high index of therapeutic safety. At the recommended dosage levels there are no contraindications. It has no cumulative effect. Patients treated for more than two years show no toxic effects attributable to the drug."

Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. 6:617 (June, 1955)

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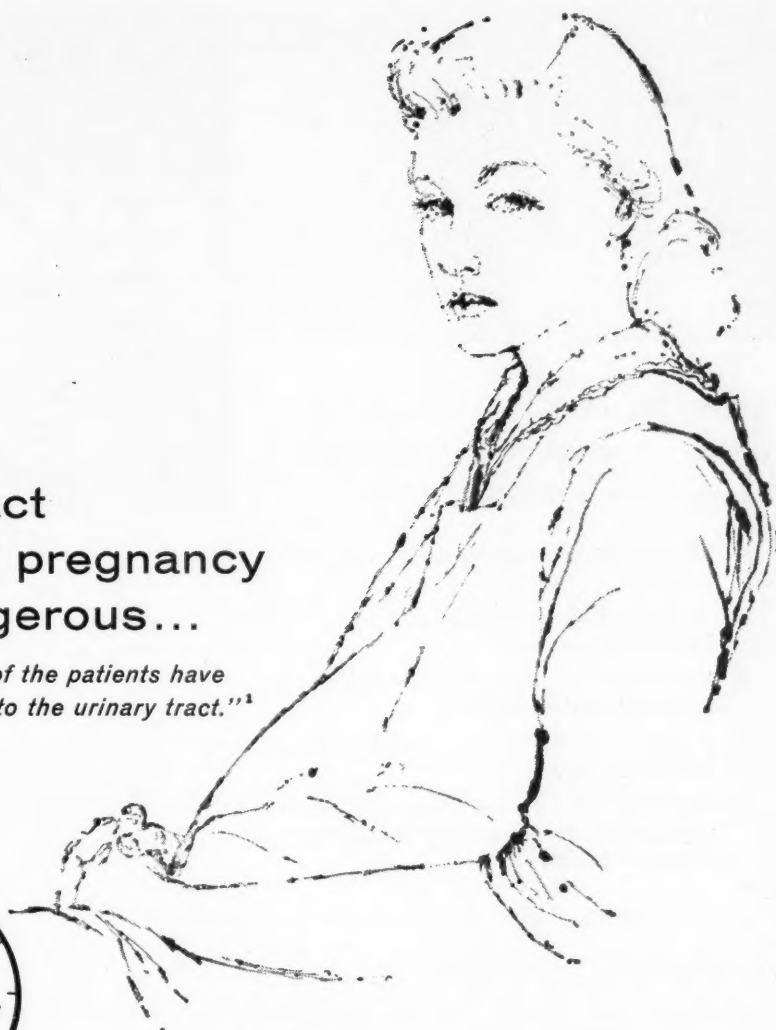
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delay is dangerous...

"Approximately one-half of the patients have
some permanent damage to the urinary tract."¹



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BRAND OF NITROFURANTOIN

first...
FOR RAPID ERADICATION OF INFECTION

Specific for genitourinary tract infections
• rapid bactericidal action against a wide
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ment for 3 days after urine becomes sterile.

SUPPLIED: Tablets, 50 and 100 mg.
Oral Suspension (25 mg. per 5 cc. tsp.).

REFERENCES: 1. Rives, H. F.: *Texas J. M.* **52**:224, 1956.
2. Diggs, E. S.; Prevost, E. C., and Valderas, J. G.: *Am.*
J. Obst. **71**:399, 1956. 3. MacLeod, P. F., et al.: *Inter-*
nat. Rec. Med. **169**:561, 1956.

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NYLMERATE JELLY . . . for vaginal discharges . . . **WARRANTS** your considered judgment. Offers **PROVEN CONTROL**

- Effective Trichomonocidal and Monilicidal action
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Availability: 3 oz. and 5 oz. tubes with applicators — 3 oz. and 5 oz. refill tubes

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. . . when vaginal douching is required.

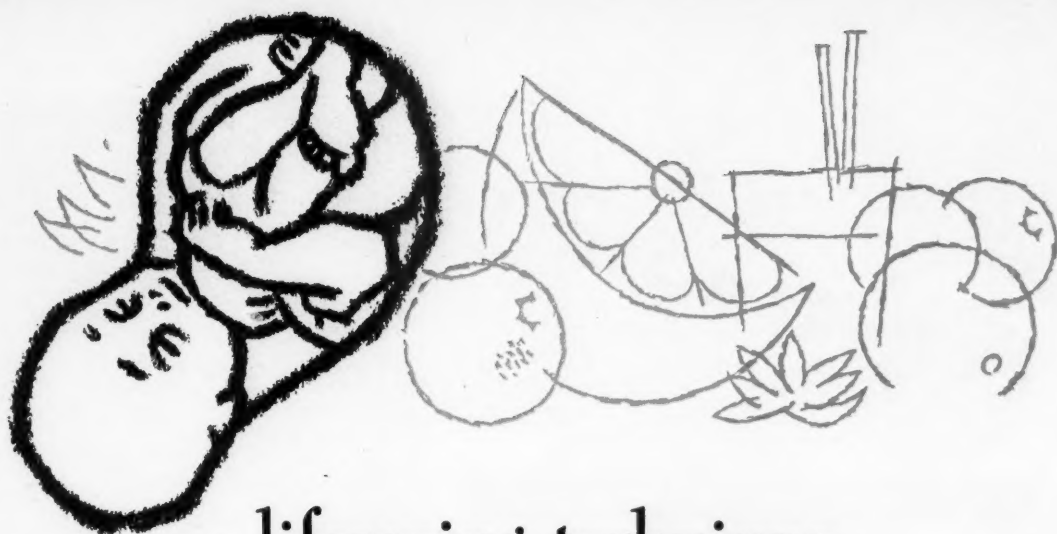


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*Abortion-prone mothers deliver live babies
in nearly 9 out of 10 pregnancies*

Reporting on 134 pregnancies in 100 habitual abortion patients, Javert* describes a management program that resulted in live deliveries in all but 16 pregnancies.

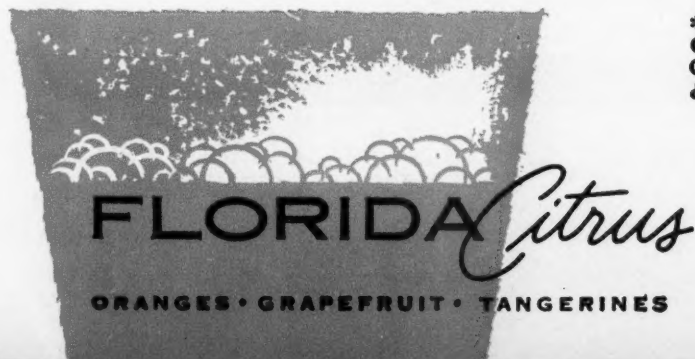
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*Javert, C. T.: Obst. &
Gynec. 3:420, 1954; Cf.
Greenblatt, R. B.: Obst.
& Gynec. 2:530, 1953.



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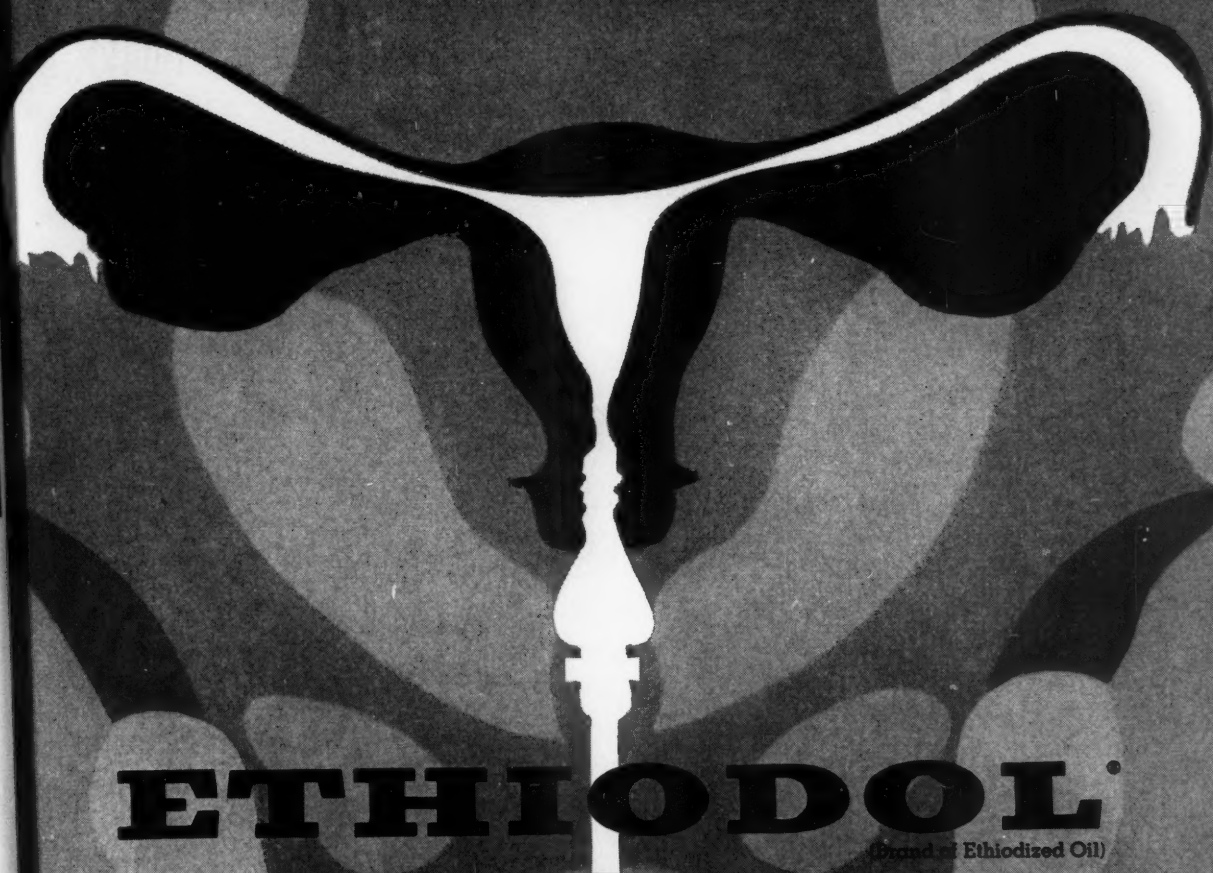
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since it is less likely to produce excessive fatigue and weakness than does reserpine."¹ Up to 80% of patients with mild labile hypertension and many with more severe forms are controlled with Rauwiloid alone.

1. Moyer, J.H.: J. Louisiana M. Soc.
108:231 (July) 1956.

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2. Wright, W.T., Jr., et al.: J. Kansas M. Soc.
57:410 (July) 1956.

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the new hormone for the treatment of hypometabolism

'Cytomel' is useful in the treatment of hypometabolism whether caused by (1) subnormal activity of the thyroid gland itself (hypothyroidism) or by (2) faulty cellular utilization of the thyroid hormone (metabolic insufficiency).

1. decreased metabolism can originate in the thyroid gland itself (hypothyroidism):

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†Other terms used synonymously in the recent literature are "euthyroid hypometabolism," "non-myxedematous hypometabolism," "pseudohypothyroidism" and "hypometabolic syndrome."



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5 meg. & 25 meg. (scored) tablets

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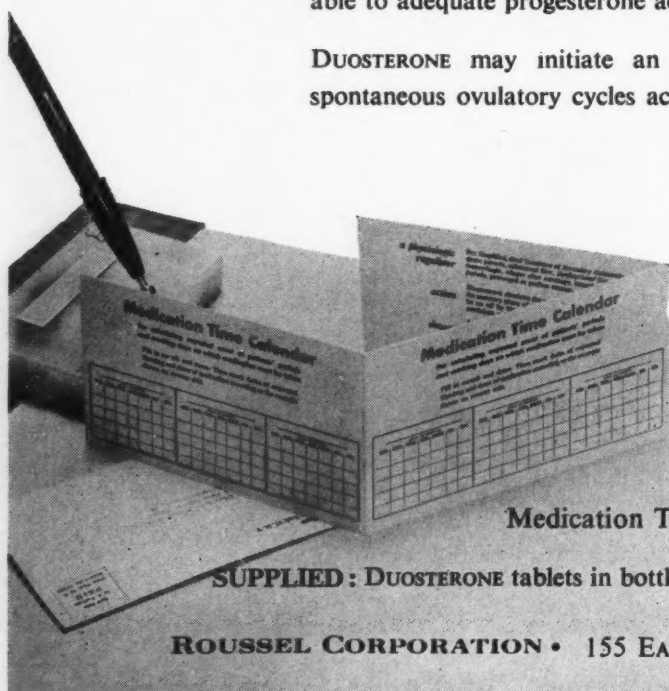
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DUOSTERONE may initiate an endocrine chain-reaction resulting in spontaneous ovulatory cycles according to the concept of Holmstrom.*

*Amer. J. Obst. & Gynec., 68:1321, 1954



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with capillary-protective factors

a precaution in normal pregnancy
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The problem of spontaneous abortion is not limited to habitual aborters. It is estimated that 10% to 20% of *all* pregnancies end in spontaneous abortion. Studies by Greenblatt,^{1,3} Javert^{4,5} and Dill² have revealed that integrity of the decidual vessels is a key to successful completion of pregnancy . . . and confirm that hesperidin complex and ascorbic acid, provided by Hesper-C Prenatal, restore and maintain capillary integrity.^{6,7}

In several groups of habitual aborters, these researchers effected substantial fetal salvage—as high as 95% in one series⁴—when Hesper-C (hesperidin complex and ascorbic acid) was added to a regimen of prenatal supplementation and therapy.

Only Hesper-C Prenatal gives your patients the extra protection of hesperidin complex and ascorbic acid, plus the established prenatal vitamin-mineral supplementation, at a nominal increase in daily cost.

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Vitamin D ₂	200 U.S.P. units
Thiamine Mononitrate	1.25 mg.
Riboflavin	0.75 mg.
Nicotinamide	5.0 mg.

Vitamin B ₁₂	0.75 micrograms
Folic Acid	0.05 mg.
Pyridoxine Hydrochloride	1.67 mg.
Calcium Pantothenate	1.0 mg.
Ferrous Gluconate (2.5 mg. iron)	21.6 mg.
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Recommended daily dose: Two capsules t.i.d.

Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

References: 1. Greenblatt, R. B.: *Obst. & Gynec.* 2:530, 1953. 2. Dill, L. V.: *M. Ann. District of Columbia* 23:667, 1954. 3. Greenblatt, R. B.: *Ann. New York Acad. Sc.* 61:713, 1955. 4. Javert, C. T.: *Obst. & Gynec.* 3:420, 1954. 5. Javert, C. T.: *Ann. New York Acad. Sc.* 61:700, 1955. 6. Barishaw, S. B.: *Exp. Med. & Surg.* 7:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: *Am. J. Digest. Dis.* 17:92, 1950.

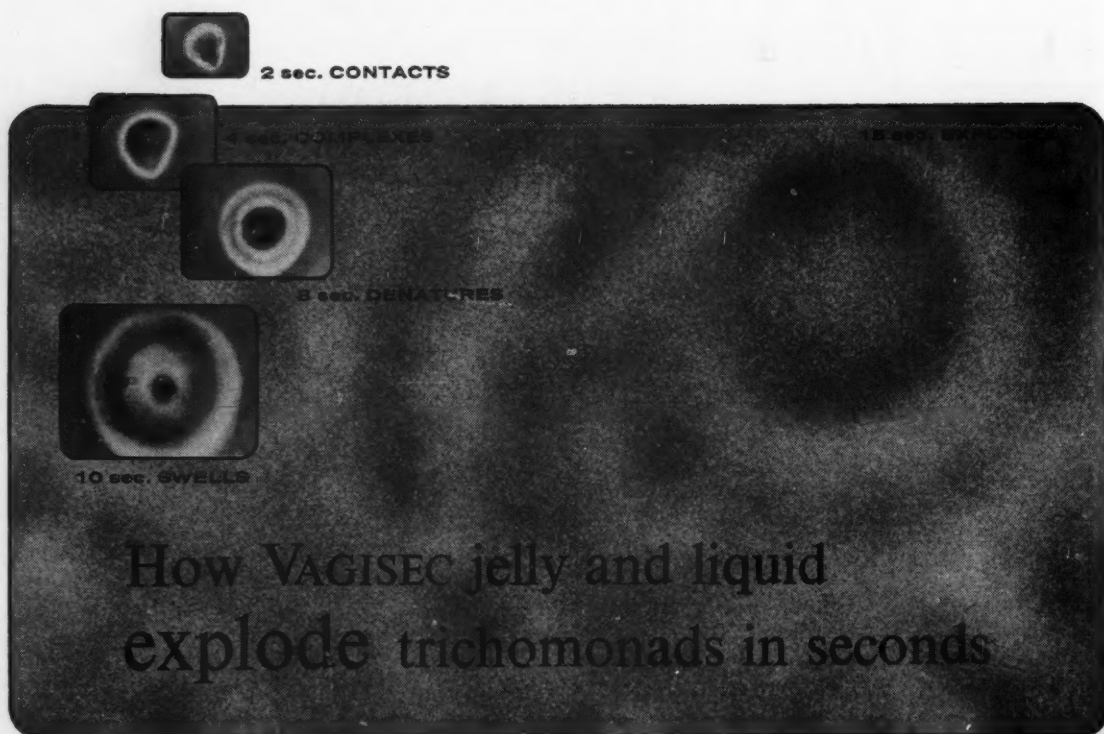
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June, 1957

Page 43



VAGINAL trichomoniasis quickly yields to VAGISEC® liquid and jelly.¹⁻⁵ These unique trichomonacides *explode* flagellates after 15 seconds' contact. Following a VAGISEC douche, VAGISEC jelly maintains trichomonacidal effectiveness 'round-the-clock. With this new approach, therapy succeeds in more than 90 per cent of cases.⁴

Research proves effectiveness—In hundreds of tests with slide preparations, mixtures of VAGISEC jelly and vigorous cultures of *Trichomonas vaginalis* have been examined under a phase-contrast microscope.^{3,6} The trichomonads *explode* and *disperse* within 15 seconds after contact with jelly—exactly like those in a VAGISEC douche solution.³⁻⁶

Explosion succeeds—VAGISEC liquid and jelly penetrate rapidly to trichomonads covered by vaginal mucus and cellular debris and *explode* them, avoiding post-treatment flare-ups.³⁻⁵ VAGISEC therapy often rids stubborn clinical cases of "trich" even after other agents fail.

Why parasites explode—A wetting agent, a detergent and a chelating agent, combined in balanced blend in VAGISEC liquid and jelly,³⁻⁵ act to weaken the parasites' cell membranes, remove waxes and lipids, and denature the protein. Then the trichomonads imbibe water, swell and explode into fragments . . . all within 15 seconds.

The Davis technique†—Dr. Carl Henry Davis, co-discoverer of VAGISEC, recommends a combination of office treatments with VAGISEC

liquid and 'round-the-clock home therapy with the liquid and jelly.³ This regimen halts vaginal trichomonal infections and ensures *continuous* control until all trichomonads are gone. For a small percentage of women who have an involvement of cervical, vestibular or urethral glands, other treatment will be required.^{1,3-5}

Re-infections can and do occur from the husband^{2-5,7,8}—Prescribing RAMSES®, high quality prophylactics, as protection against conjugal contagion ensures husband cooperation. Most of them know and prefer RAMSES—the one with "built-in" sensitivity. RAMSES are superior, transparent rubber prophylactics, naturally smooth, very thin, yet strong. At all pharmacies.

Active ingredients in VAGISEC liquid: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Boric acid, Alcohol 5% by weight.

References: 1. Decker, A., and Decker, W. H.: Practical Office Gynecology, Philadelphia, F. A. Davis Company, 1956. 2. McGoogan, L. S.: J. Michigan M. Soc. 55:682 (June) 1956. 3. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, W. F. Prior, 1955, vol. 3, chap. 7, pp. 23-33. 4. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955. 5. Davis, C. H.: J.A.M.A. 157:126 (Jan. 8) 1955. 6. Molomut, N., Port Washington, N. Y.: Personal communication (Jan.) 1957. 7. Draper, J. W.: Internat. Rec. Med. 168:563 (Sept.) 1955. 8. Feo, L. G., et al.: J. Urol. 75:711 (Apr.) 1956.

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the problem of the "vegetable" patient

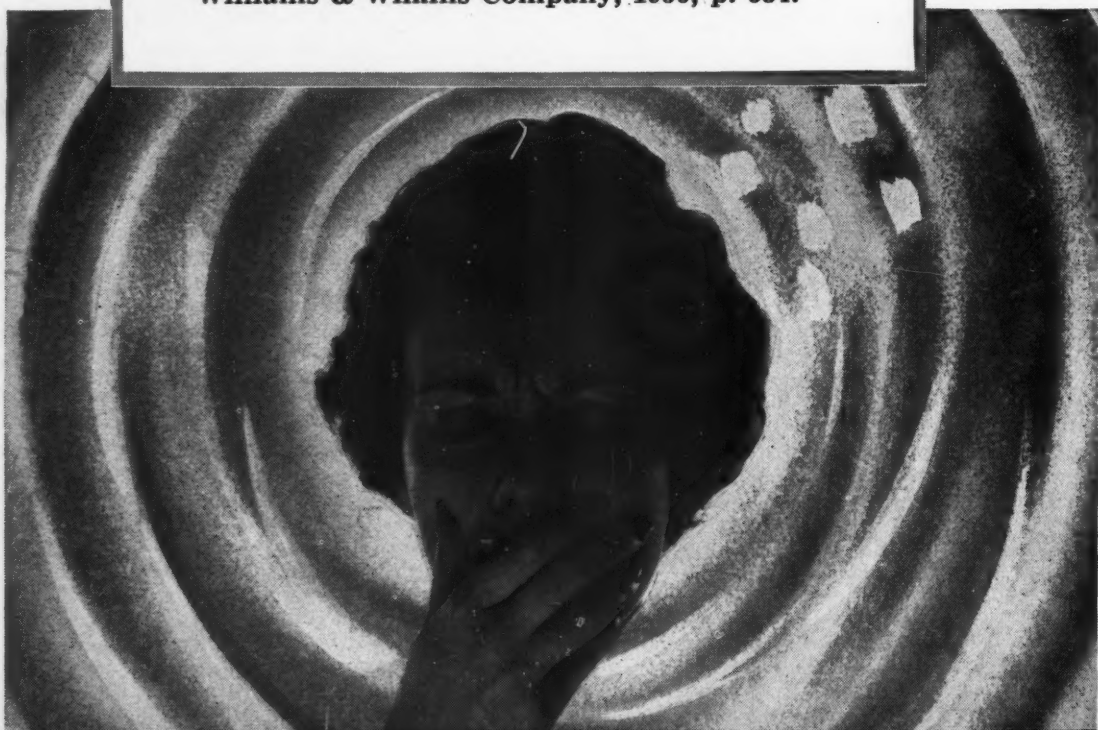
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Rehfuss, M. E., and Price, A. H.: *A Course in Practical Therapeutics*, ed. 3, Baltimore, The Williams & Wilkins Company, 1956, p. 534.



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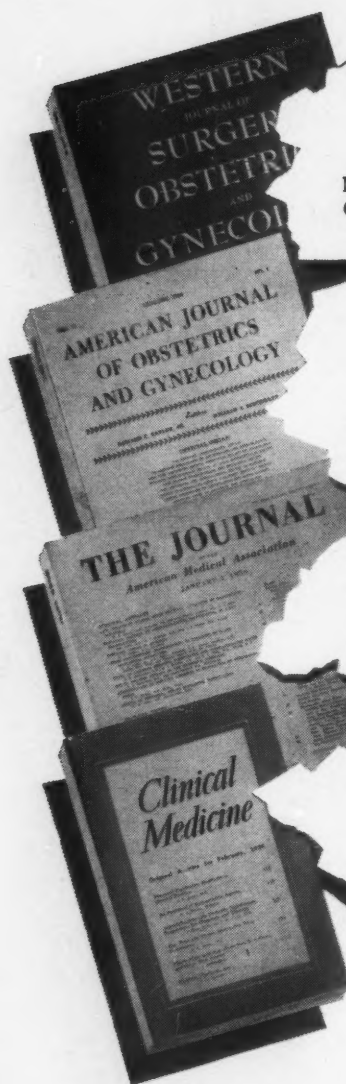
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Karnaky, K. J.: Western Journal of Surgery,
Obstetrics and Gynecology, Vol. 51, pp. 150-152.

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Thornton, M. J.: American Journal of Obstet-
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Dickinson, R. L.: The Journal of the Ameri-
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Sackren, H. S.: Clinical Medicine, Vol.
46, pp. 327-329.

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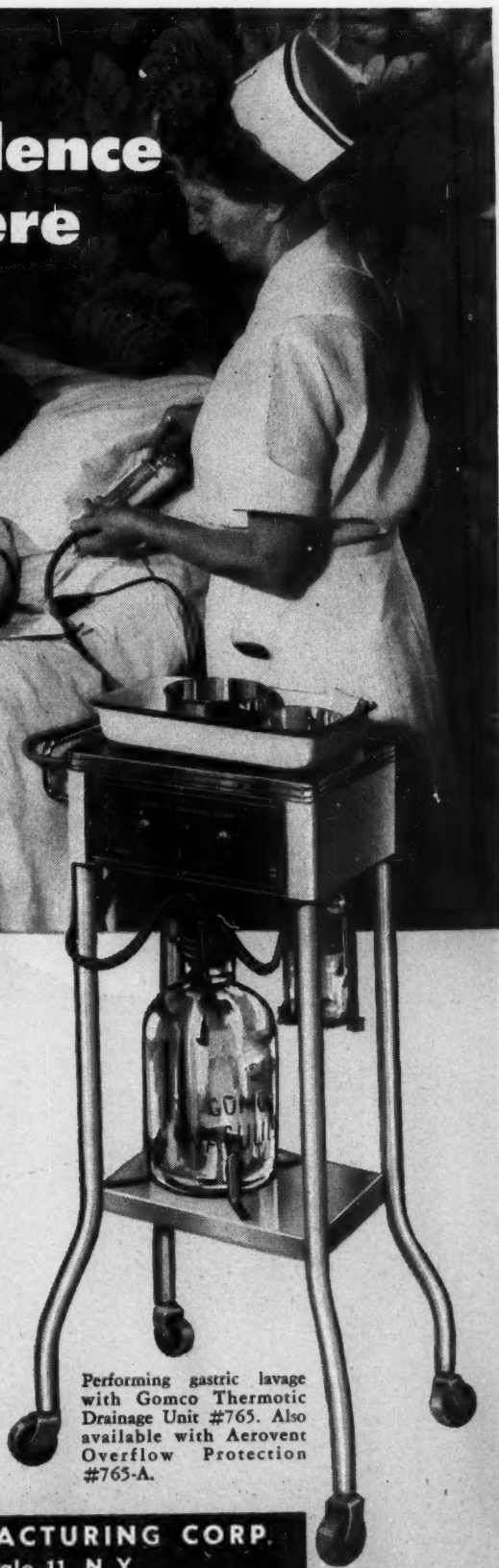
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and SHERWIN A. KAUFMAN, M.D., F.A.C.S.

*Associate Attending in Obstetrics and Gynecology, Beth Israel Hospital, New York City;
Medical Director, Planned Parenthood of Manhattan and the Bronx, New York
City; Diplomate, American Board of Obstetrics and Gynecology*

WITH its "corridor consultation" approach, this highly useful book gives immediate recommendations for both diagnosis and treatment of commonly met gynecologic problems. Organization of the subject by presenting symptoms, and handy tables of differential diagnosis, form a dependable desk reference for every general practitioner and gynecologist. Advanced medical students, too, will appreciate the simplicity of style, as well as the diagnostic tables. It is based on experiences gained in teaching gynecology to postgraduate students and general practitioners, and on knowledge gained in extensive, successful practices.

In text and illustration, the reader learns how to recognize symptoms and how to reach a proper diagnosis quickly. For each condition a single form of therapy, proved effective in actual practice, is detailed.

The discussions of symptoms, diagnosis and treatment constitute the greater portion (Part I) of this concise, yet comprehensive book. Part II is an unusual gallery of gynecologic drawings with full legends that describe important diagnostic and therapeutic technics. *The authors first tell you what to do, then show you how to do it!* All illustrations emphasize anatomy and procedures described, without non-essential detail.

To maintain the easy readability of the text, the more specialized aspects of gynecology have been wisely presented as a separate and unique annotated bibliography. These up to date clinical abstracts in Part III amplify the text for those who wish to explore the subject more deeply. Controversial issues and differing points of view are in this section. This is truly "Modern Office Gynecology" as every physician should know it.

218 Pages, 5 $\frac{1}{4}$ " \times 7 $\frac{1}{4}$ ".

47 Illustrations.

\$4.50

(Published January, 1957)

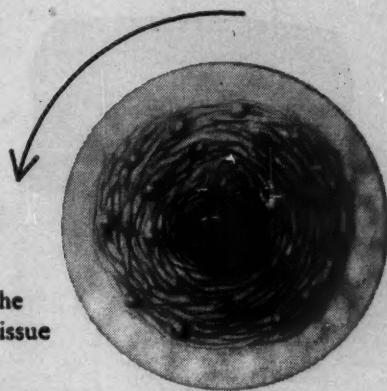


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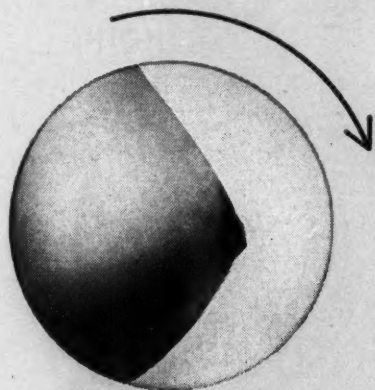
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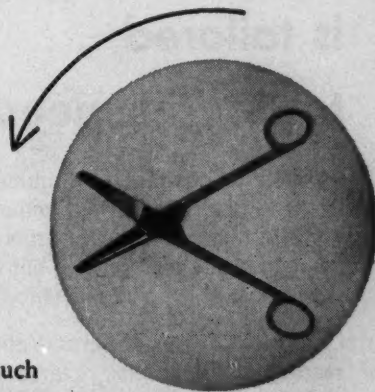


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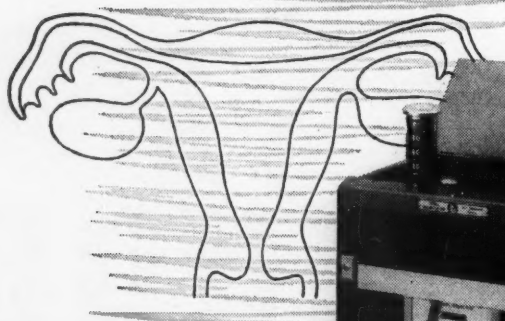
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Sacks, M. S.: Ann. Int. Med. 42:458, Feb., 1955.

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total	6.8%	17.7%	15.2%	37.7%

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¹ Anz, U.E., and Smith, L.J.: Am. J. Obst. & Gynec. 71:1242 (June) 1956.

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References: 1. Statist. Bull. Metrop. Life Insur. Co., vol. 37 (Oct.) 1956. 2. Kiser, C. V.: Milbank Mem. Fund Quart. 33:393 (Oct.) 1955. 3. College Study Report: Population Bull. 11:45 (June) 1955. 4. Tietze, C.: Proc. 3rd Internat. Conf. Planned Parenthood, 1953. 5. Pärnanen, P. O.: Ann. chir. et gynæc. Fenniae Suppl. 43:315, 1954.

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References: (1) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: *Progress in Hematology*, New York, Grune & Stratton, Inc., 1956, vol. 1, p. 25. (2) Gaisford, W., and Jennison, R. F.: *Brit. M. J.* 2:700 (Sept. 17) 1955. (3) Wallerstein, R. O.: *J. Pediat.* 49:173, 1956. (4) Sturgeon, P.: *Pediatrics* 18:267, 1956. (5) Jennison, R. F., and Ellis, H. R.: *Lancet* 2:1245 (Dec. 18) 1954. (6) Scott, J. M., and Govan, A. D. T.: *Brit. M. J.* 2:1257 (Nov. 27) 1954. (7) Grunberg, A.,

Clinical improvement paralleled this response. Premature infants and surgical cases were similarly benefited. IMFERON gave "...all the advantages of transfusion or intravenous therapy without the disadvantages."² There were no side effects in any of the infants treated. Wallerstein³ confirmed these results, furnishing evidence that IMFERON is well absorbed and appears in the bone marrow 12 to 24 hours after injection. Results are equal to those with intravenous saccharated iron oxide without the unpleasant side effects. Sturgeon⁴ showed that the first year's iron requirements in infancy can be supplied with three injections of IMFERON.

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and Blair, J. L.: *A.M.A. Arch. Int. Med.* 96:731, 1955. (8) Millard, J. B., and Barber, H. S.: *Ann. Rheumat. Dis.* 15:51, 1956. (9) Baird, I. M., and Podmore, D. A.: *Lancet* 2:942 (Nov. 6) 1954. (10) Cappell, D. F.; Hutchinson, H. E.; Hendry, E. B., and Conway, H.: *Brit. M. J.* 2:1255 (Nov. 27) 1954. (11) Stevens, A. R.: *A.M.A. Arch. Int. Med.* 96:550 1956.

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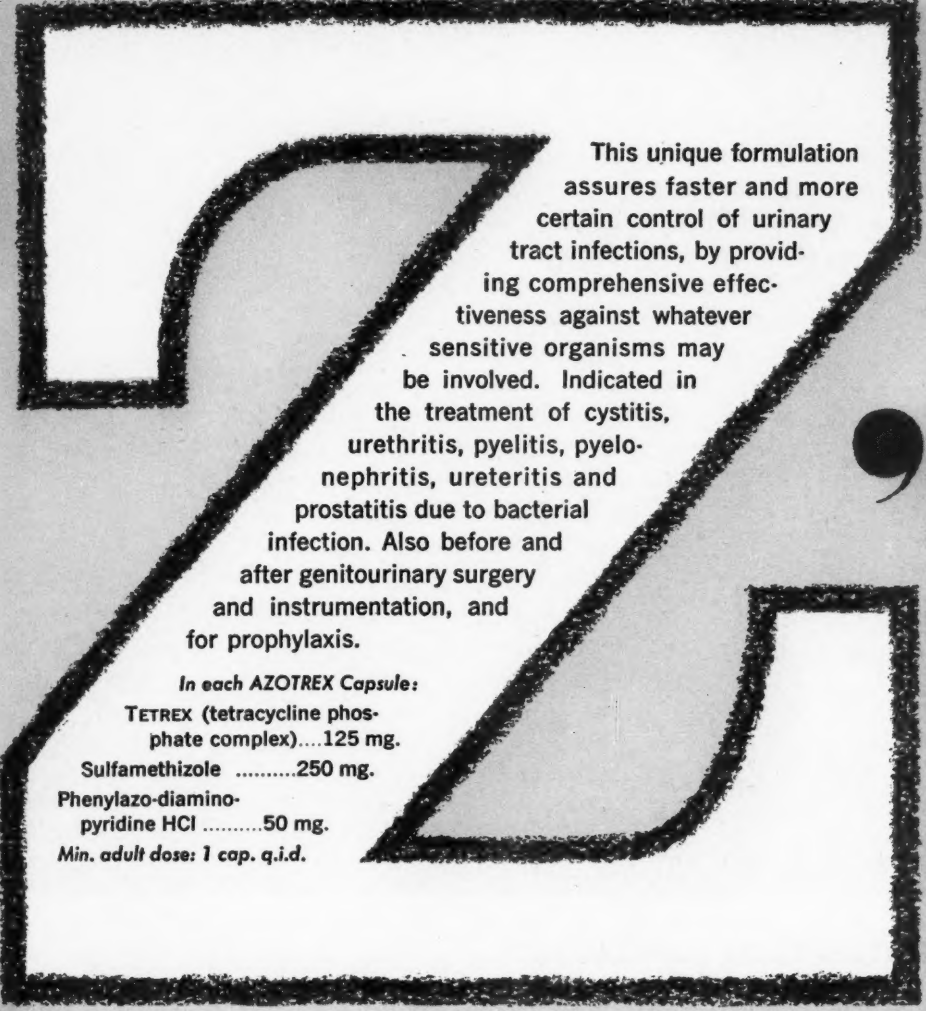
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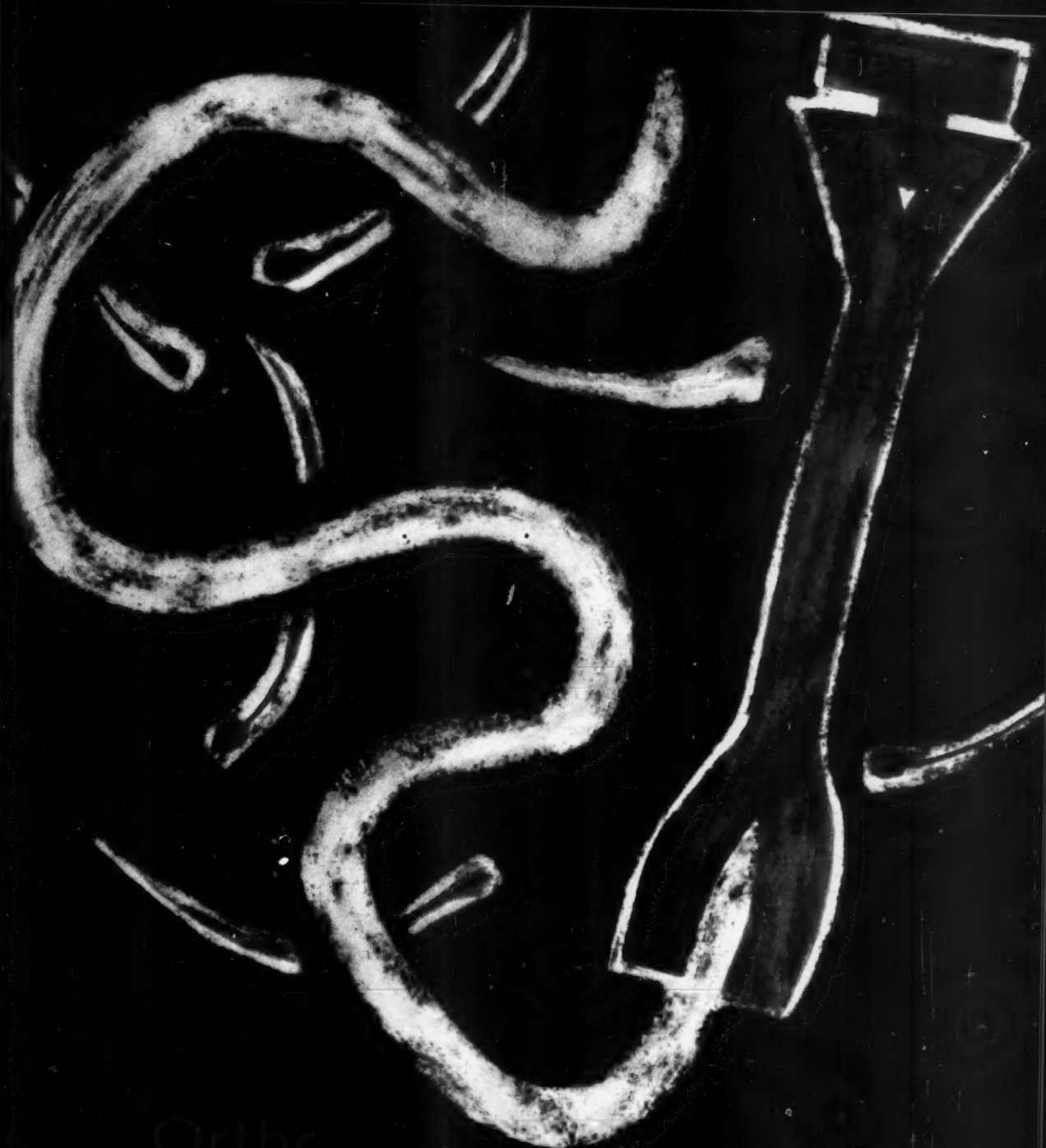
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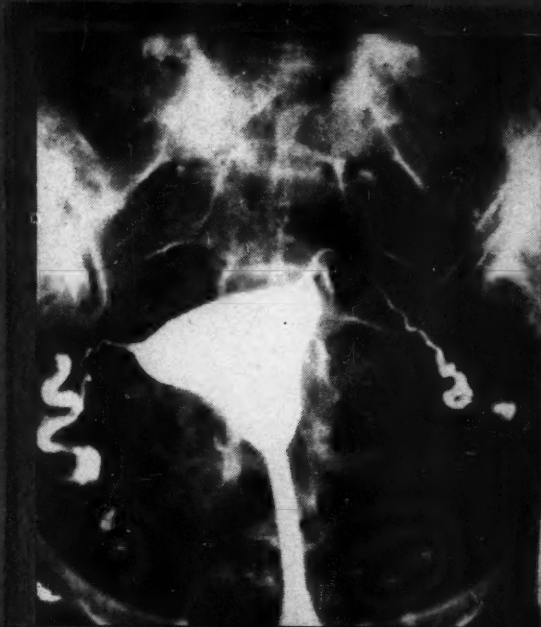
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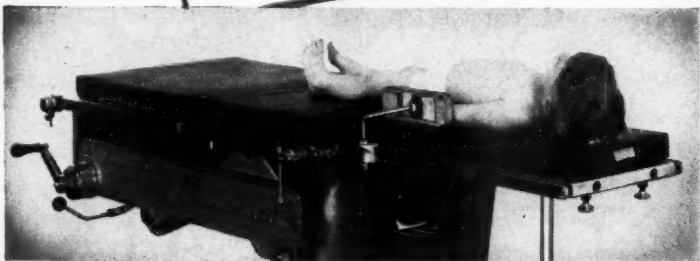
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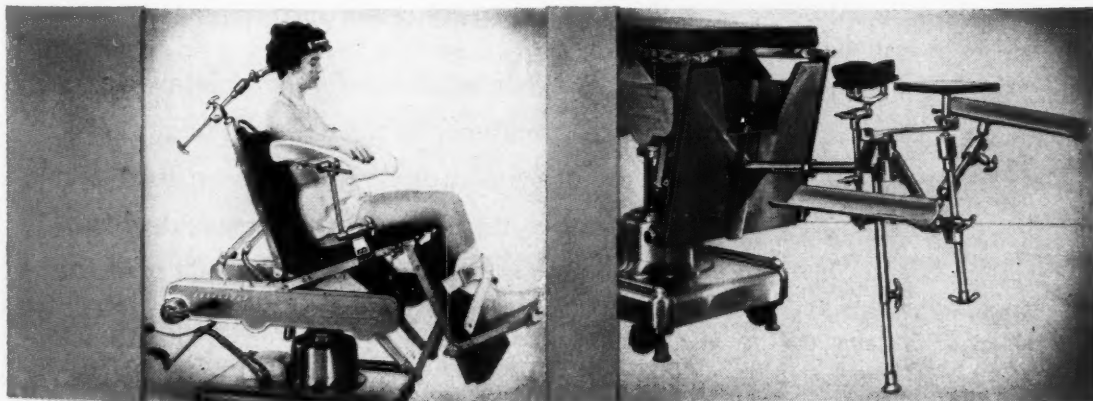
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CONSIDERATIONS ON OBSTETRICS AND OBSTETRICIANS*

Presidential Address

J. A. RENÉ SIMARD, M.D., QUEBEC, QUEBEC

(From the Department of Obstetrical Pathology, Laval University)

OBSTETRICS, doubtless because it was practiced by midwives, has long been a quite humble art. Nowadays it still remains, in the minds of many, a poor relation of medicine and surgery. Sometimes a good friend will repeat the sally: "If your son is intelligent, let him be a physician; if he is clever, let him be a surgeon; if he is neither, let him be an accoucheur!"

Yet obstetrics today is no longer a facile art to be exercised without risks by some old woman who has learned only by experience. It has become an exact and difficult science, requiring from those who practice it the intelligence of the physician and the dexterity of the surgeon. No other medical discipline has more quickly applied the discoveries of recent years and none has seen the rate of morbidity and mortality shrink more rapidly.

If, however, obstetrics has progressed, the obstetrician has not, and he must not change. He should keep his former virtues, since he has the same duties in the midst of the same difficulties.

There was a time, I have been told, when only the life of the mother counted; then we became civilized to the point where one took also into account the life of the child; now, it is sometimes alleged, only one survival is important—that of the "accoucheur!"

*Presented at the Twelfth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Murray Bay, Quebec, June 8, 9, and 10, 1956.

As have other members of the medical profession, we have felt ourselves, of late, the target of a spirit of revolt and of the social demands characteristic of our contemporary society. We are accused of having forgotten, in the love of comfort, our sense of devotion; of having made, through our commercialism, a money-making business out of an honorable profession; of having lost, by our excessive specialization, all personal contact with the patient, and the communion between the suffering spirit and the ailing body. Further, we have been accused of having acquired a contempt for human sufferings and human life! It is true that we may give this impression to the uninitiated, who see us from afar and do not know anything about our inner lives. Let us say that a few of us may have merited some of these reproaches.

The great French surgeon, Jean Gosset, said—at the First International Convention of Medical Morality, held in Paris last September—“Whosoever would venture to compare what little he knows with all he should know, who would reflect on what little all know compared to what all ignore, would never again take a bistoury in his hand without the pangs of a sterilizing anguish which, itself, would be morally to be condemned.”

When the time to act comes, one must forget that he is ignorant of so many things, so as not to paralyze his actions. At other times, he must remember it and make it a point of duty to add to his knowledge.

Surely, the only thing that can never be held as a reproach to us is that we have been too learned and too versed in our profession! I do not mean this in the sense of “à la mode,” fascinated by all innovations, partial to every recent method. I give here to the word “learned” a higher signification. One must constantly recall that all that is new is not necessarily good, that all that is written is not definitively true, that what is published is usually the result of a few successful experiences, that publication is often done more out of vanity than in real concern for the future of obstetrics.

I believe that people have a right to scorn the physician petrified in his outmoded routine, in his excessive fear of intervention. Actually, nobody believes that things will always correct themselves. On the other hand, an exaggerated desire for experimentation, a self-confidence without limits, and an optimism that fears nothing are more in their place in the laboratory, where they can work marvels, than at the bedside of a woman, where the physician holds in his hands the lives of two human beings.

Maternal and fetal deaths are not always avoidable, but sometimes one may find in these traces of carelessness, incompetence, and also, sometimes, precipitateness and excesses in the treatment. The obstetrician must be neither a useless spectator nor an injurious actor in the drama of birth!

We have a profession in which it is difficult to keep a good conscience. At times we must regret having acted, and at other times having abstained from intervention. Sometimes we know we have been too hardy or too timid, too confident or too pessimistic, too compassionate or too cruel.

Nothing better demonstrates the vicissitudes of the practice of obstetrics than its renunciation by the general practitioners when they reach the time

when they must take greater care of their health, or, more simply, when they arrive at a level of fortune where they can relinquish part of their activities. Many reasons motivate the surrender of this part of general practice. Nocturnal rising is cheerfully supported if the physician is young, in good health, and not fatigued. When enthusiasm disappears, when sickness or fatigue comes, who can tell of the anguish and distress he will suffer from repeated calls? It is worse if he has to fight against a winter storm, in the middle of the night, when every means of transportation may be half paralyzed. If the car does not start, or if it slides and sticks fast in the snow bank, who will help the doctor lost in the storm and the cold, when everything that lives is warmly sheltered and sleeping? The obstetrician must, nevertheless, act quickly, because somewhere someone is waiting with impatience and possible criticism, and delay may be the cause of serious complications. . . . One must have lived these moments to understand their distressing reality!

If one were free to refuse this or that call, the burden would not be so great, but, morally, the obstetrician does not possess that liberty. There is, in effect, between the doctor and the expectant mother a tacit contract. (I am not speaking here of the woman who, in the course of delivery, calls the doctor for the first time. To that woman, the doctor is obliged to render help only according to the general laws of charity and medical ethics.) I have in mind the typical patient, the woman who has come periodically for prenatal consultations. The obstetrician is bound to this patient, and this bond constitutes, perhaps, the most arduous part of his duties, since it restricts his liberty to a great extent.

Do you propose an agreeable evening with friends, the audition of a concert, a game of golf, a reception with your kinsfolk, or something of the sort? It is most probable that you will be needed and that you will have to go. . . . Should you, forgetting your preoccupations for an instant, play amateur gardener, painter, or mechanic, an urgent call will get you with dirty hands and muddy clothes. What kind of trip will you make if you leave behind you many worried women, or if, when you return, you are looked upon as a man who has failed in his principles of honor and loyalty? Will you enjoy the hours of relaxation of a week end or an excursion when you have the sense of stealing these hours from those to whom your every moment is consecrated? Your necessary vacations must be arranged many months in advance so as to be able to notify your patients at their first consultation with you that you will not be able to assist them during that period. The obstetrician works twenty-four hours a day, since he must be on call from midnight to midnight each day.

In order to reserve a few hours to themselves, some obstetricians may form a group and take their turns in answering urgent calls. This kind of practice may be the future answer to the troubles of the obstetrician. Much water will flow under many bridges, however, before this type of organization can become general, when all women agree to be assisted indifferently by doctor so-and-so, whom they have chosen, before whom they have unveiled their

bodies and their souls, in whom they have placed all their confidence, or doctor so-and-so, whom they know but little and who may or may not be sympathetic to them. In their eyes, this is the concretion of their fear of the robot doctor treating the robot patient.

Few are those among us who are participants in this kind of practice. Yet we must admit that we all benefit already—thanks to modern transportation, to our hospitals, to our specialized nurses, to our anesthetists—from a marked alleviation of the harshness of our profession.

Nevertheless, we remain overstrained people, and our kind of life provides neither for health nor for the best conditions of work. When one's time is so broken by calls, visits, fatigue, and worries, all serious work, involving reflection and concentration, is done at the cost of untold effort.

This question of study and scientific production is also intimately linked with the rates of emolument. If the obstetrician demands three or four hundred dollars for each delivery, as is done in some American centers, he will be in a position to accept only a few scores of patients a year. He will have enough to live well and also the time to give to his professional development, to research, or, in a word, to study. If, on the contrary, his rates are in the order of a few tens of dollars, he will have to multiply the number of his patients and to renounce in good part theoretical work and serious scientific production. Such is the dilemma we are in. Must we ask for antisocial emoluments and pursue eminent science, or accept smaller emoluments with reduced knowledge?

This matter of emoluments cannot be a matter of indifference to a physician who has a developed social sense. I realize that in certain large cities one can ask for seemingly fantastic fees; the fortunes are many and the children are rare! But let us place ourselves in a district where the mean revenue is not high and where children come frequently, and it becomes evident that to ask much from these people in helping them to reproduce is an anti-natural and antisocial act.

Morality speaks to a doctor in a case like this. In fact, the obstetrician must frequently engage in a dialogue with morality, because morality is very much concerned with obstetrics. The great dilemma is not, as the uninitiated may imagine, "Must I sacrifice the life of the mother or the child?" We never now sacrifice the life of anyone, but our consciences may still ask: Can abortion be prevented; is the fetus alive; is the maneuver feticide; is it abortive; will the death of the child result directly from our voluntary act; must the woman be castrated; is such an intervention purely complacent, and what risks will it entail?

Here, in their primary simplicity, we have the important questions which our consciences must consider. Yet how great are the complexity and the multiplicity of cases that are encountered in one's career! Solutions will often have to be reached in the physician's own conscience because the urgency will not allow for consultations.

There is also much that one might say about the moral integrity that must be possessed by the physician who receives the intimate confidences of so many young women. Woe to him who cannot make an abstraction of the woman in his patient! What strict fidelity to our professional oath is essential to the proper exercise of the obstetrical art! One must be discreet by temperament and impose an extreme self-discipline against the temptation to reveal even the absurd or the commonplace, the divulging of which would at the very least make of us a very interesting drawing-room companion.

The obstetrician must be kind and patient. He must alleviate the greatest of physical pains. Let him bring to that task infinite compassion and comprehension. Let him not add to the miseries of the woman by his hardheartedness or his cruelty. Let him never tire of waiting. His impatience to leave his patient for his pleasure or his relaxation must never be the cause of precipitate gestures or intemperate maneuvers.

With these womanly virtues, the obstetrician must combine in addition science and judgment, hardiness, composure, strength, and manly health. Decisions must often be made instantly, when they cannot await consultation with a confrere or a manual. If one chooses a bad solution, or if, thinking of the good solution, one is not cool enough to act at the proper moment, one may kill by his abstention or by his act, and with his own hands.

I have outlined here with such severity the qualities and duties of the obstetrician, the merit and the austerity of his art, that one may ask why so many men who are not possessed of an angelic nature are still dedicated to it. One practices obstetrics by necessity, by devotion, or by choice, or for all of these various motives combined in various proportions, and depending on whether one is an obstetrician occasionally or exclusively. One cannot be a country doctor without practicing obstetrics, for in many towns and cities one cannot enter into general practice without assisting women at the delivery bed. The older general practitioner may try to abstain from it, but then devotion to former patients prevents his refusing the pressing requests of future mothers. As for those who are obstetricians as specialists, they may have reached their position through the fortuitous play of circumstances without knowing very well on what an arduous road they were setting out, but they cannot remain in the profession except by choice.

It is truly possible to find in the art of obstetrics great happiness, notwithstanding fatigue and servitude, the length of the days and the shortness of the nights, because this branch of medicine brings the physician not to the bed of death but to the bed of life. There is indeed in the life of the doctor no more agreeable moment than that in which he realizes that through his acts a new member has been given to the family and to society. Pain and anguish give place to rest and quiet and happiness, and he takes leave of a smiling and grateful couple.

This is certainly more pleasant than visits to the sick, where it always takes longer to bring back a smile. Sickness, even after restoration to health,

leaves behind a measure of sadness. The patient feels debilitated, diminished; he is afraid of a recurrence and he knows well that he will not always conquer illness.

According to the Gospel, the woman who has given birth rejoices because she has given a new man to the world, and all her kin rejoices with her. Such consolation also is found in the bonds of gratitude and affection of the patient toward him who has been the support, the comfort, the savior. What joy to see children grow whom one has really put into the world, particularly if they are here only through one's skillfulness, without which they would never have opened their eyes! One must also take into account the satisfaction felt in the exercise of a science which is, like surgery, its parent, much more precise than other medical disciplines, and with results more tangible and immediate. So often we must take the primary role and make Nature herself our helper.

Such, ladies and gentlemen, are the magnitude and the misery of the obstetrician's life. Taking a stand contrary to the sentiments expressed by those who vilify the medical profession, I want to be to you the spokesman of all the children who owe their lives to you and of all the mothers you have succored. In the name of those who ignore what they owe to you or who, through timidity or ingratitude, have not expressed their appreciation, I want to thank you and all those who, like you, have sacrificed their pleasure to the joy of others, their rest to the peace of others, their health to the life of others, their own life to the birth of a new generation.

EXENTERATION OPERATIONS IN THE TREATMENT OF ADVANCED PELVIC CANCER*

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(From the Department of Obstetrics and Gynecology of the New York Hospital and Cornell University Medical College)

IN 1948 Brunschwig¹ reported his experiences with 22 pelvic exenteration operations for far-advanced or recurrent pelvic malignancy. Since that time there has been a marked increase in the number of these radical procedures reported in the literature. Brunschwig, Jordan, and Pierce² in 1950 described the anterior pelvic exenteration operation and reported on 21 patients. Brunschwig and Pierce³ published their data in 1950 on 65 patients with total exenterations and 35 with partial exenterations. In the same year, Parsons and Bell⁴ reported their experiences with 29 patients. In 1951 Bricker and Modlin⁵ described in detail their method of exenterations and the results in 32 cases. Brunschwig and Daniel⁶ recorded the largest series in the literature with 202 total and 113 anterior exenterations in 1954. In the same year the former author⁷ reported the results of operation on 77 patients with carcinoma of the cervix who had recurrent or persistent disease six months or more following treatment by radiation, surgery, or a combination of both. Brunschwig and Murphy⁸ submitted their findings and results in 57 patients who had radical hysterectomies and 17 who had pelvic exenterations for recurrent endometrial carcinoma. Parsons,⁹ Bricker,¹⁰ Ulfelder,¹¹ Ingersoll,¹² and Brunschwig¹³ presented detailed descriptions of their operations in 1954. In 1955, Parsons¹⁴ reported on 86 patients with carcinoma of the cervix treated with exenterations, including 28 patients who had been operated upon over five years before. Schmitz,¹⁵ discussing Parsons' paper, related his experiences with 37 patients, and Smith¹⁶ mentioned 18 total exenterations on his service. Emge,¹⁷ however, pointed out in the same discussion that nearly 15 per cent of the patients in the California State Tumor Registry with untreated carcinoma of the cervix lived five years or more. In 1956, Thyssen¹⁸ reported on 72 patients with carcinoma of the cervix and endometrium, among whom 10 had total exenterations, 3 anterior exenterations, and 59 radical hysterectomies.

Our experience has been limited, but it represents a record in some detail of the patients with advanced disease in whom this operation has been performed. The series may not be large enough to have great statistical significance, but this is not the prime purpose of this report. It is a critical review of this type of therapy in a large university hospital with

*Address of the Guest Speaker, presented at the Twelfth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Murray Bay, Quebec, June 8, 9, and 10, 1956.

a well-balanced obstetrical and gynecological service where treatment of cancer is but one phase of activity. As further justification for recording these data, there are complete follow-up observations on all but one patient who was well and apparently free of disease when she left the country some four and one-half years following operation.

Material

From 1948 through 1954 there have been 23 pelvic exenterations performed at the New York Lying-In Hospital. Twenty of these were pavilion and 3 private patients. Twenty-two of these procedures have been partially or completely done by the senior author. In a considerable number of additional cases (approximately 20) the procedure was abandoned following exploratory operation because the disease was found to extend beyond the pelvis, or for other reasons was considered unjustifiable. During the same period of time there have been 122 radical hysterectomies and pelvic lymphadenectomies performed (Table I).

TABLE I. RADICAL PELVIC SURGERY AT THE NEW YORK LYING-IN HOSPITAL, 1948-1955

YEAR	RADICAL HYSTERECTOMIES	EXTENERATIONS	
		TOTAL	ANTERIOR
1948	10	2	4
1949	26	4	2
1950	14	2	—
1951	12	2	—
1952	14	2	—
1953	17	2	1
1954	19	2	—
1955	10	—	—
Total	122	16	7

The total exenteration operation in 16 patients consisted of a resection of the lower ureters, bladder, vagina, uterus, adnexa, lower sigmoid colon, rectum, pelvic peritoneum, and pelvic lymph nodes. In 10 of these patients the ureters were transplanted to the skin, and in 6 into the bowel with the creation of a wet colostomy.

The anterior exenteration in 7 patients consisted of a resection of the lower ureters, bladder, vagina, uterus, adnexa, pelvic peritoneum, and pelvic lymph nodes. The ureters were implanted into the sigmoid in all 7 cases.

TABLE II. TYPE OF LESION, TYPE OF PROCEDURE EMPLOYED

	NO.	EXTENERATIONS	
		TOTAL	ANTERIOR
Carcinoma, cervix			
Stage II	10	7	3
Stage III	4	3	1
Stage IV	4	4	—
Carcinoma, endometrium	3	—	3
Carcinoma, urethra	1	1	—
Carcinoma, ovary	1	1	—
Total	23	16	7

In Table II are listed the primary lesions and the type of procedure employed. The cervical cancers were classified when first seen and retained in that classification irrespective of subsequent persistence, spread, or recurrence of disease. All of the patients with carcinoma of the cervix had received

radiation therapy. Radical surgery was never employed as a primary form of treatment in any patient with carcinoma of the cervix, endometrium, or ovary. Except for the one case of carcinoma of the urethra, all the exenterations were done following failure of either radiation therapy, radiations and less radical surgery, or surgery alone. These procedures were never offered purely as palliation, but were done only with the hope of cure of the disease.

Twenty of the patients had had some form of previous radiation and 3 had none (Table III). These latter included the patients with carcinoma of the ovary and urethra, and one with carcinoma of the endometrium.

TABLE III. PREVIOUS X-RAY AND RADIUM THERAPY

External irradiation and vaginal cone	10
External irradiation and radium	6
External irradiation alone	3
External irradiation, radium, and vaginal cone	1
Total	20

Thirteen of the patients had one or more pelvic operations prior to the exenterations. Two had radical hysterectomies and pelvic lymphadenectomies at the New York Lying-In Hospital just one year prior to the more radical procedures. Three had previous hysterectomies for carcinoma of the endometrium while 10 had had no previous surgery.

Age.—Table IV indicates the age at the time of the pelvic exenteration. The youngest patient was 34 and the oldest 72, with an average age of 50.5 years.

TABLE IV. AGE AT THE TIME OF EXENTERATION

Less than 40	3
40-49	7
50-59	9
60-69	3
Over 70	1
Total	23

Preoperative Investigation

All patients had a complete history and physical examination, examination under anesthesia, proctoscopy, cystoscopy, urine cultures, intravenous pyelograms, blood chemistry determinations, chest films, bone x-rays for metastases, and a barium enema prior to the operation. In addition, the need and the extent of the contemplated operation were explained in detail to both the patient and the responsible members of the family. The possibilities of complications were reviewed and the permanency of the anatomical changes were stressed.

TABLE V. PREOPERATIVE EVALUATION—EXAMINATION UNDER ANESTHESIA

	CARCINOMA			
	CERVIX	ENDO-METRIUM	OVARY	UTERUS
Extension to vagina with crater	13	1	1	1
Parametrial spread	9	1	—	—
Spread to pelvic wall, unilateral	8	—	—	1
Rectal and bladder involvement	5	—	—	—
Bladder involvement	4	—	—	—
Spread to pelvic wall, bilateral	3	—	—	—
Rectal involvement	2	—	1	—

Four of the 23 patients had a nonfunctioning kidney, and one showed a hydroureter and hydronephrosis prior to operation. In all others the upper urinary tracts were within normal limits. Five showed evidence of invasion of the bladder mucosa. Six others showed fixation of the base of the bladder, but not invasion of the mucosa. Examination of the rectum and sigmoid showed one patient with a polyp, one with diverticulosis, and one with the rectosigmoid narrowed by an extrinsic mass. All other proctoscopic and barium enema examinations were negative.

Table V summarizes the findings at the examinations under anesthesia prior to operation.

Operation

General anesthesia was employed in all cases. A hypotensive state was maintained during only one operation. An intraspinous transverse incision was used in 14 cases and longitudinal incision in the remainder.

The average operating time for the total exenteration was 7 hours and 29 minutes, with the shortest 4 hours and 30 minutes and the longest 9 hours and 40 minutes. The average total operating time for the anterior exenteration was 6 hours and 38 minutes, with the shortest 5 hours and the longest 7 hours and 30 minutes.

On the examination under anesthesia prior to the exenterations, 16 of the 18 patients with carcinoma of the cervix, one with carcinoma of the endometrium, and one with carcinoma of the urethra were thought to have lateral extension of their disease. Eleven were interpreted as having either unilateral or bilateral spread out to the pelvic walls. At the operating table, however, in 7 of the 11 cases, no difficulty was encountered in achieving a cleavage plane at the side wall of the pelvis. In 3 some difficulty was met in establishing a cleavage plane. One had fixed induration at the right pelvic wall and at operation it was necessary to cut through tumor at this point. In one instance there was no preoperative evidence of lateral spread, but it was necessary to remove periosteum from the bony side wall at the time of operation because of extension of disease.

No attempt will be made to describe the technique of the procedures, as they did not differ significantly from that reported by Brunschwig,^{1, 2, 13} Parsons,⁹ or Bricker,¹⁰ except that 17 were done as abdominal-perineal procedures and 6 were done completely from above.

TABLE VI. BLOOD REPLACEMENT

C.C.	NO.
1,000-1,500	3
1,600-2,000	5
2,100-2,500	2
2,600-3,000	6
3,100-3,500	1
3,600-4,000	3
4,100-4,500	2
Above 4,500	1
Total	23

Table VI indicates the blood infused. The smallest amount was 1,500 c.c. and the largest was 5,500 c.c. with an average of 2,935 c.c. Accurate knowledge as to blood loss was maintained at all times by measuring aspirated blood and weighing sponges in order that replacement would continually equal the loss.²⁰

Pathology

The type of lesion and the pathology at the time of exenteration are shown in Table VII. It is apparent that in most of these cases the tumor was far advanced. One patient had a positive bladder biopsy just prior to the exenteration, but at the time of operation no residual tumor could be found. We were in error in clinical interpretation of induration in one patient, believing that the induration represented carcinoma. Pathological examination showed this induration to be inflammation and necrosis with only degenerated cancer cells in the cervix.

TABLE VII. PATHOLOGY AT THE TIME OF THE EXENTERATIONS

CARCINOMA	PATHOLOGY
<i>Cervix, Stage II.—</i>	
Case 1	Metastases to bladder.* No residual tumor
Case 2	Metastases to vagina, rectum, and bladder
Case 3	Lymphatic metastases
Case 4	Residual tumor. Metastases to uterus, vagina, rectum, and bladder
Case 5	Residual tumor. Metastases to right iliac, left obturator nodes, parametrium, rectum, bladder, and lymphatics
Case 6	Metastases to vagina
Case 7	Metastases to parametrium and rectum
Case 8	Metastases to vagina, rectum, urethra, and lymphatics
Case 9	Metastases to hypogastric nodes, blood vessels, vagina, and parametrium
Case 10	Degenerated cells in cervix with marked necrosis and infection
<i>Cervix, Stage III.—</i>	
Case 1	Residual tumor. Metastases to vagina
Case 2	Residual tumor. Metastases to bladder, uterus, nodes, and parametrium
Case 3	Residual tumor. Metastases to bladder, uterus, vagina, parametrium, and lymphatics
Case 4	Residual tumor. Metastases to lymphatics and nodes
<i>Cervix, Stage IV.—</i>	
Case 1	Metastases to bladder and nodes
Case 2	Residual tumor. Metastases to uterus, vagina, lymphatics, and bladder
Case 3	Residual tumor. Metastases to vagina, bladder, myoma, and lymphatics
Case 4	Metastases to bladder, vagina, rectum, blood vessels, lymphatics, piriformis muscle, and sacrospinatous ligament
<i>Endometrium.—</i>	
Case 1	Metastases to bladder
Case 2	Metastases to vagina
Case 3	Metastases to bladder, urethra, and vagina
<i>Urethra.—</i>	
Case 1	Metastases to ovary and nodes
<i>Ovary.—</i>	
Case 1	Metastases to vagina, rectum, and lymphatics

*Biopsy of bladder one week prior to exenteration.

Postoperative Course, Care, and Complications

Accurate weight of the patients was determined daily and frequent electrolyte and other blood chemical studies were done. Gastric or upper small bowel suction was maintained. Intake and output measures were recorded and electrolyte and fluid requirements were planned each day in advance, based on the data and the experience of the previous 24 hours. Antibiotic and anticoagulant therapy was employed. Hospitalization was provided on a floor devoted almost entirely to the care of pelvic neoplastic disease, and the nurses were specially trained for this function. We cannot overemphasize the importance of their devotion and skills in the successful management of these patients.

Postoperative Phase.—Table VIII lists the postoperative complications which were encountered in these patients. As can be seen, the highest percentage of complications were in connection with urinary tract stasis, dilatation, and infection.

TABLE VIII. POSTOPERATIVE COMPLICATIONS

COMPLICATION	NO.	PER CENT
Urinary tract infections	18	78.2
Bilateral hydronephrosis	17	73.9
Febrile postoperative course	16	69.5
Paralytic ileus	5	21.7
Low-grade fever	4	17.3
Unilateral hydronephrosis	3	13.0
Wound eviscerations	2	8.6
Thrombophlebitis	2	8.6
Myocardial infarction	1	4.3
Total	68	

Seven patients (30.4 per cent) required subsequent operative procedures before discharge from the hospital (Table IX).

TABLE IX. SUBSEQUENT OPERATIONS PRIOR TO DISCHARGE

Revisions of ureterostomies	3
Secondary closure	2
Incision and drainage of pelvic abscess	1
Examination under anesthesia only	1
Packing of pelvis	1
Perineotomy	1
Incision and drainage of periureteral abscess	1
Total	10

There was one postoperative death which occurred 6 days following a total exenteration. Of the remaining 22 patients, the shortest postoperative hospital stay was 23 days and the longest was 111 days, with an average of 45.4 days.

Follow-up

Complete follow-up observations were possible on 22 of the 23 patients. The one who was lost had an anterior exenteration on April 7, 1948, for a recurrent adenocarcinoma of the endometrium with extension to the bladder. She was followed for 4½ years during which time she developed and was treated for a primary carcinoma of the breast. She was last seen in 1952 at the age of 73 in good condition with no evidence of further recurrence of either malignancy. At this time she then returned to her native Norway.

Of the 23 patients 16 (69.5 per cent) are dead. One is alive with evidence of widespread metastases, one is lost to follow-up, and 5 (21.7 per cent) are alive without evidence of tumor. Two of the 10 (20 per cent) operated on five years ago or more are still living (Table X).

Living.—The 6 living patients have adjusted to their surgery rather well (Table XI). One is well 7 years and 8 months following an anterior exenteration for persistent carcinoma of the cervix. At the time of operation she had evidence of metastases to the bladder. Another is well 7½ years following a total exenteration. The pathological examination showed marked necrosis and infection, but only degenerated carcinoma cells in the cervix. She has had readmissions for the purpose of creating an artificial vagina. At the present time she is gainfully employed and in good health. One patient is surviving and well 3 years and 8 months following a total exenteration for a Stage III cervical carcinoma. Pathological examination showed extensive

TABLE X. FOLLOW-UP RESULTS ON 23 EXENTERATIONS

	NUMBER	ALIVE				DEAD		LOST	
		WITHOUT TUMOR		WITH TUMOR					
		NO.	%	NO.	%	NO.	%	NO.	%
Total exenterations	16	4	25.0	1	1.5	11	68.7	—	—
Anterior exenterations	7	1	1.2	—	—	5	71.4	1*	1.2
Total	23	5	21.7	1	4.3	16	69.5	1	4.3

*Observed 4½ years. No evidence of tumor when last seen.

TABLE XI. SURVIVORS OF THE 23 PELVIC EXENTERATIONS AND TIME OF SURVIVAL UP TO JUNE, 1956

1 living and well	7 years, 8 months
1 living and well	7 years, 7 months
1 living (terminal)	4 years, 10 months
1 living and well	4 years, 8 months
1 living and well	3 years, 8 months
1 living and well	2 years, 2 months
Proved 5 year survivals	2 (20%)

TABLE XII. SURVIVING LESS THAN ONE YEAR AFTER PELVIC EXENTERATION

DISEASE AND STAGE	POSTOPERATIVE HOSPITAL STAY	SUBSEQUENT COURSE	SURVIVAL
Cervix, Stage II	6 days	Died on 6th day	6 days
Carcinoma, endometrium	28 days	Discharged after exenteration to a terminal care home	2 months
Carcinoma, urethra	47 days	Course after discharge unknown. Notified of death	3 months
Cervix, Stage IV	73 days	Unable to get out of bed at home. Admitted 4 months following exenteration and died in 3 days	4 months
Cervix, Stage II	58 days	Admitted 4 weeks after discharge for transfusion. Readmitted 3 months after surgery with increasing weakness. Remained in hospital 1 month and died	5 months
Cervix, Stage III	61 days	Readmitted in 4 months with severe vomiting. Remained 13 days. Readmitted in 7 months with vomiting and remained 7 days. Readmitted in 7½ months with abscess of abdominal wall with gross carcinoma in abscess. Deteriorated rapidly and died in hospital	9 months
Cervix, Stage III	23 days	Did well for 3 months, then admitted in severe pain requiring intrathecal alcohol and x-ray therapy. Became grossly incontinent of bowel and bladder. Remained in hospital 1 month and then discharged. Continued in pain at home and was readmitted 10 months following surgery for 13 days. Readmitted 1 month later with intractable pain and died in the hospital	1 year

residual tumor and metastases to the vagina, uterus, and parametrium. Except for periodic clinic visits for cleansing and changing the ureteral catheters, she is well and able to carry out her household duties. One other is in good health 2 years and 2 months after a total exenteration for Stage III carcinoma of the cervix. The specimen revealed metastatic carcinoma of the vaginal vault, the left parametrium, and the left hypogastric nodes. She was admitted one month postoperatively with left pyeloureteritis with stenosis of the ureter which responded to catheterization and antibiotics.

One patient is alive, but in the terminal stages of her disease with widespread metastases 4 years and 4 months following a total exenteration for Stage III carcinoma of the cervix. She did well until January, 1956, when a solitary metastasis was found in the left mandible, followed by rapid spread to the ribs, pleura, and lungs.

TABLE XIII. SURVIVING MORE THAN ONE BUT LESS THAN TWO YEARS AFTER PELVIC EXENTERATION

DISEASE AND STAGE	POSTOPERATIVE HOSPITAL STAY	SUBSEQUENT COURSE	SURVIVAL
Cervix, Stage II	42 days	Did well for 6 months. Had a recurrence with severe pain requiring intrathecal alcohol. Remained in hospital for next 4 months and died there	13 months
Cervix, Stage IV	28 days	Course unknown. Notified of death	15 months
Cervix, Stage II	43 days	Did well for 1½ years except for recurrent urinary tract infections. Admitted with pain in thigh and large abdominal mass. While hospitalized, had a large bowel hemorrhage requiring 4,000 c.c. of transfused blood. Developed a fecal fistula. Sent home on morphine sulfate after 33 hospital days. Had another bowel hemorrhage at home and died	17 months
Cervix, Stage IV	52 days	Did well for 1½ years. Then admitted with edema. Developed fecal fistula. Exploration and an ileocolostomy performed. Died after 3 months in hospital	18 months
Cervix, Stage II	67 days	Did well for 6 months except for difficulty with ureteral catheters. Admitted after 9 months with fecal fistula. Resection of small bowel performed and patient discharged after 1 month. Readmitted 1 month later with a left ureteral skin abscess which was drained. Spent 2 months in hospital. Readmitted 1 month later for recurrence of abscess. One year following exenteration developed second fistula and severe pain. Intrathecal alcohol block done and patient discharged after 1 month. Admitted to terminal care home and remained there for 6 months until her death	21 months
Cervix, Stage II	31 days	Admitted within 3 months with local recurrence to mons pubis. Did well but then lost to follow-up. Notified of death	22 months
Cervix, Stage II	36 days	Did well for 9 months. Developed perineal hernia which was repaired with difficulty. Spent 3 months in hospital. Discharged and then lost to our follow-up. Notified of death	22 months

One patient is alive and well 4 years and 8 months following a total exenteration for carcinoma of the ovary. At the time of operation, adherent nodules were found in the pelvis, vagina, and sigmoid. She has returned to work in a responsible secretarial capacity and has adjusted well to the ureteral cutaneous transplants and the colostomy. It is significant to note that this patient informed us prior to her operation that she had resigned her position and would never resume her former activities. In addition to a full-time position, she is now attending to her home and garden as well as caring for her elderly mother.

Dead.—The subsequent course of the 16 patients who have succumbed has not been as uneventful. One patient died on the sixth postoperative day, a surgical mortality of 4.3 per cent. Seven (43.7 per cent of the deaths) were dead within one year and another 7 died before the end of the second year. One lived 4 years and 1 month and another 4 years and 4 months before succumbing to their disease. Tables XII, XIII, and XIV give a résumé of the subsequent courses of these 16 patients.

TABLE XIV. SURVIVING OVER FOUR YEARS AFTER PELVIC EXENTERATION

DISEASE AND STAGE	POSTOPERATIVE HOSPITAL STAY	SUBSEQUENT COURSE	SURVIVAL
Cervix, Stage IV	47 days	Did well for 2 years. Admitted with gastroenteritis. Did well for another year and then admitted with cough and pleural effusion. Spent 15 days in hospital. Readmitted in 1 month and received x-rays to chest. Readmitted in 1 month with abdominal pain and stayed 7 days. Readmitted 3 years after operation with shortness of breath and in obvious terminal stages. Transferred to terminal care home where she remained for 6 months requiring frequent thoracentesis	4 years and 1 month
Carcinoma, endometrium	51 days	Readmitted in 3 months for left ureteral skin transplant. Spent 3 months in hospital. Did well for 1 year and then readmitted with pubic pain. Nodule removed from inferior ramus of pubic bone which was carcinoma. Did well for next 2½ years when she was admitted with intestinal obstruction. Exploration and an ileotransverse colostomy performed. Did poorly postoperatively and died in hospital	4 years and 4 months

Cause of Death.—Thirteen of the 16 had evidence of recurrent carcinoma at the time of death. Two died at home presumably with recurrent carcinoma. One died on the sixth postoperative day and autopsy failed to show evidence of carcinoma. Autopsy studies were performed on 7 patients. The findings are summarized in Table XV.

TABLE XV. FINDINGS AT AUTOPSIES OF 7 PATIENTS WITH PELVIC EXENTERATIONS

Carcinoma	6
Pyelonephritis	6
Pneumonia	3
Pelvic abscesses	3
Intestinal obstruction	2
Fistulas	2
Venous thromboses	2

Comment

These operations have been confined to those patients who had recurrences after receiving either irradiation, irradiation and surgery combined, or surgery alone. We believe the basic treatment of carcinoma of the cervix to be radiation from high-energy external sources and radium or its equivalent. In advanced primary cervical disease we have employed radiation as the initial therapy in the belief that with some decrease in the size of the tumor the operation may be somewhat easier, less hazardous, and the chance of spread of the disease at the time of operation less likely. We can well conceive of occasions, however, when primary surgery might be the procedure of choice. Carcinoma of the endometrium is treated primarily by operation, including a "wide" hysterectomy and pelvic (selective or total) lymphadenectomy. If there has been extension beyond the endometrium, this has been followed with deep x-ray therapy.²¹ The management of recurrence is individualized, depending on the size and location of the tumor. Except in one case, pelvic exenteration has played no role in our treatment of ovarian carcinoma. In the one instance referred to, the patient had had very extensive primary surgery for her tumor with rather prompt evidence of persistent progressive disease. All examinations indicated, when we first saw her, that the disease was confined to the pelvis. Subsequent events strongly indicate that the procedure was justifiable.

Brunschwig¹³ includes in his indications for total exenterations, patients with carcinoma of the cervix, uterus, vagina, vulva, and rectum, with spread to the bladder and rectum and surrounding areas either previously untreated or recurrent after treatment. Parsons¹⁴ stated that 70 per cent of the cases in his series were done following recurrence after irradiation. Twenty-four per cent of his patients with tumors classified as Stage III or IV, however, were offered pelvic exenteration as the primary treatment and his indications for the procedure have now changed to include it as the therapy of choice for far-advanced disease. Bricker¹⁰ includes in his indications carcinoma of the rectum, cervix, uterus, or vagina recurring after irradiation therapy.

In his original publication, Brunschwig¹ said the operation was conceived as a palliative measure, but that at the present time it is done only rarely for this indication.¹³ Parsons⁹ states that total exenteration should be undertaken with the basic idea of cure, not palliation. Bricker¹⁰ also feels that the operation should not be attempted when there is little hope of survival. We are in complete accord with this point of view.

Most authors feel the age of the patient must be taken into serious consideration and Bricker⁵ has listed being over 60 as a contraindication. Chronological age does not always convey all necessary information regarding degenerative processes. One patient at 65 may appear, act, and live like a patient much younger in years, or on the other hand like a person much older in years. We believe that one must individualize each patient as far as the aging phenomenon is concerned. Four of our patients were over 60 years of age at the time of operation.

The preoperative evaluation of these patients is time consuming and expensive. An important aspect of preoperative preparation is the psychological preparation. The patient should understand fully what the operation entails and must be willing to accept the risks involved. The husband, or other responsible members of the family, should also be fully informed regarding the procedure and its long-term implications. A detailed search must be made for remote metastases prior to the operative procedure. Extensive physical examinations as well as numerous chemical, nutritional, and hematological studies must be done in order to evaluate the suitability and the patient's ability to withstand such surgery. At the New York Lying-In Hospital, the laboratory facilities are located within the physical plant of the obstetrical and gynecological division in charge of a full-time clinical biochemist. Intravenous pyelograms and cystoscopy are essential in the evaluation of these patients. Bricker,¹⁰ on the other hand, does not routinely do cystoscopies and does not find a detailed knowledge of the urinary tracts of great importance. Parsons⁹ added, "the finding of a non- or poorly functioning kidney on one or both sides does not necessarily deny the patient the chance of surgery."

The examination under anesthesia is perhaps the most important preoperative test. It consists of a thorough abdominal as well as a bimanual vaginal and rectovaginal examination. Oftentimes the findings are most revealing compared to the information obtained with the patient awake. Many authors have commented on the difficulty of evaluating the extent of the disease. The important factor to determine is the degree of lateral fixation and this at times is discovered only at abdominal exploration. Ideally, the patient with extension into the bladder or rectum without lateral spread is the best candidate for the exenteration procedure. The significance of lateral extension to the pelvic wall in any instance is not that the operation cannot be performed, but that subsequent recurrence is probable. Parsons⁹ feels that the fascia overlying the levator muscles and the side wall of the pelvis are highly resistant to invasion by the malignant process and that the lateral extension is far more likely to be due to radiation or inflammatory fibrosis than cancer. Brunschwig¹³ states that limited invasion of the bony pelvic girdle need not always be a contraindication, since involved portions of the bone can be removed. We have occasionally removed some periosteum, but have not resected bone.

The operation necessitates a highly trained team. The anesthesiologist should be familiar with the patient and select those anesthetic agents best suited to the individual concerned. The nursing personnel should be specially trained for this type of work. Capable assistants should be available to combat any of the emergencies, especially hemorrhage, which might arise during the procedure. Brunschwig and Daniel⁶ had 6 deaths in the operating theater due to uncontrolled shock and their average blood replacement was 3,500 c.c. In this series the average blood loss was 3,000 c.c., but in the past few years

with the use of hypotensive drugs, the blood loss has become considerably less. The dissection required is meticulous and the surgeon must be at all times minutely aware of the anatomy of the area in which he is working.

We have transplanted the ureters to the skin or the sigmoid. The former has been the most successful procedure, but the most important postoperative complications have been urinary tract infections and dilatation of the ureters and the kidney pelves. This has been true of all series published. We have had no experience as yet with utilizing a segment of ileum as a bladder substitute as described by Bricker,^{10, 22-25} or of using the descending colon as described by Parsons,^{9, 14} with the creation of a transverse colostomy for fecal drainage and the distal segment for urinary drainage. Perhaps one of these methods will provide a better solution to this most difficult problem.

The postoperative management is so varied and complicated that it is impractical to discuss it in detail. As Parsons stated, "the patient subjected to this procedure has had about all she can stand. The emphasis in postoperative management is on prevention and early apprehension of complications." Here again the value of a laboratory and a clinical biochemist available at all times is of the greatest importance. Specialists in all branches of medicine, and a complete armamentarium of drugs, fluids, and equipment are essential in their care.

It is evident that most patients must anticipate some immediate postoperative complications. An average postoperative stay of a month and a half when looked at from the financial aspect alone is an appalling one. When one considers all the efforts, discomfort, and sacrifices involved on the part of the hospital personnel, the patient, and the family, one marvels, not that there have been so few, but that there have been as many of these operations performed.

Brunschwig's⁶ five-year survivals are recorded as 12 per cent with 12 patients alive after five years out of 104 operations from 1947 to 1950. Parsons'¹⁴ five-year survivals number seven out of 28 (25 per cent). In our small series, the five-year survival rate has been 2 out of 10 or 20 per cent. Statistics can never indicate, however, the full extent of what this procedure means in terms of "living" versus "survival." For a limited number of patients the long-term "living" has appeared to be good, but for a much larger number the "survival" has been extremely difficult and discouraging. The great majority of the deaths occurred during the first two postoperative years and were equally distributed during these years. Although autopsies were performed on only one-half of these patients, it appears that all died of cancer; and, in retrospect, for the most part they were not suitable candidates for the procedure. It is significant that at the time of operation it was thought that in nearly all instances the tumor was completely removed. Parsons'¹⁴ experience has been similar in that those who died during the first 12 months had recurrent bouts of pyelonephritis or intestinal obstruction requiring multiple hospital admissions. He also found, as we did, that those who survived over two years, only to die later, had returned to active life until a few months before death.

Brunschwig points out that these procedures are not necessarily completely futile. These patients have widespread or recurrent cancer, and any procedure, regardless of the extent, which can return a certain number of "doomed" individuals to an even near-normal life may be a worth-while procedure. Emge's¹⁷ figure of 15 per cent five-year cures in untreated carcinoma of the cervix is based on all cervical cancers and not just the extensive disease found in the cases under discussion. This procedure is not one to be attempted by all gynecological surgeons in any and every hospital. It should be undertaken only in those institutions capable of providing the complicated care and by those surgeons trained to perform the extensive surgery.

Summary and Conclusions

1. The literature on pelvic exenteration has been reviewed.
2. A detailed description of the age, past radiation and surgical history, preoperative evaluation, operative and postoperative courses, pathology, and follow-up of the 23 patients who have had pelvic exenterations at the New York Lying-In Hospital has been presented.
3. This form of therapy may be indicated in a very limited number of patients with advanced pelvic cancer after failure of radiation, radiation and surgery, or surgery alone. Such a procedure should be undertaken only with the basic idea of cure, not palliation.
4. The preoperative evaluation of each case must be meticulous and complete. It should include a thorough search for local and distant recurrence and metastases, using all the modern diagnostic methods available. A careful abdominal and combined vaginal and rectovaginal examination under anesthesia is one of the most important preoperative requirements.
5. The patient with spread to either bladder or rectum or both, but no lateral spread of the disease, is the best candidate for the operation. The final decision as to operability in a case with apparent spread to the lateral pelvic wall must, however, be determined at the time of laparotomy.
6. The postoperative care and course are difficult and fraught with many complications requiring the full facilities of a large institution. The most difficult task is the preservation of adequate urinary output and the avoidance of urinary tract infection and damage.
7. One must take into consideration the patient's age, physical and psychological condition, the natural history of the disease, the operative mortality, the chance for cure, and the surgeon's ability to carry out the necessary procedures and willingness to care for any of the complications before offering this type of surgery.
8. The institution involved must be willing to assume a financial burden, provide the necessary nursing, medical, diagnostic, and therapeutic facilities, and assume a major responsibility for rehabilitation, readmission, and perhaps long-term care of these unfortunate individuals.

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CORTISONE AND SPECIFIC ANTIBIOTICS FOR RESISTANT PELVIC INFECTIONS*

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SINCE 1950, in Ottawa, we have treated 45 carefully selected cases of resistant pelvic inflammation with a combination of the anti-inflammatory adrenal cortical steroids and proved specific antibiotics. It must be remembered that at the beginning of this period cortisone was thought to be specifically contraindicated in the presence of infection.

Our criteria for selection of cases and the details of procedure have been described adequately elsewhere. The purpose of this brief paper is to outline our present point of view, not as final conclusions but as preliminary results which others may try to duplicate and improve.

Although our first cases were reported in March, 1952,¹ the only others reported, as far as a thorough search of the world literature can disclose, are still too few to allow this method to be regarded as standard procedure.²⁻⁵

The theory upon which our therapy is based is that when pelvic infections are treated inadequately with specific antibiotics or are treated too late excessive granulation tissue is laid down. Buried in this shelter, the offending bacteria are no longer accessible to circulating antibiotics, leukocytes, opsonins and agglutinins. The body reaction can itself become a disease. Masses of granulation tissue can cause menorrhagia, metrorrhagia, pelvic pain which varies with its location in the pelvis, dysmenorrhea, dyspareunia, and anemia. The patient assumes the typical picture of the "pelvic cripple" who is told to go home and let the infection cool off until she can return for hysterectomy. There were 5 patients who, before we started combined treatment, had developed bowel obstruction, and one, bilateral hydronephrosis. All 5 of these patients had received adequate specific and supportive treatment. Before "combined" treatment their condition was, however, deteriorating rapidly.

The anti-inflammatory adrenal cortical steroids, cortisone, hydrocortisone, prednisone, and prednisolone have all been used in heavy doses to dissolve the complicating granulation tissue and allow circulating, proved specific antibiotics to kill the bacteria as they are freed. For brevity, the term cortisone in this paper will apply to all the previously mentioned steroids. Cortisone is used intramuscularly or orally in doses of 300 mg. the first day, 200 mg. the next, and 100 to 150 mg. daily thereafter. Hydrocortisone has been used intravenously or by mouth and prednisolone by mouth only, in comparable doses. Prednisolone is our drug of choice when bowel obstruction due to ileus or mechanical block has occurred because of its lack of tendency to electrolyte imbalance. The intravenous form which is to be available shortly will be a great help.

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The way these steroids dissolve solid masses of granulation tissue has to be observed to be believed. A solid, tender, hot mass becomes soft and porridgelike in 48 hours and often is gone completely by the fifth day. The hand of the amazed examiner then feels a soft, movable, definable, painless pelvis. The patient herself, who up until this time has feared the painful exploring pelvic examination, is the first to confirm that she is on the road to recovery.

The cornerstone of this approach is the absolute proof that we can attack the liberated bacteria with a proved specific antibiotic. A mistake in this respect could obviously be fatal. This can be avoided by "in vitro" antibiotic sensitivity tests, aerobic and anaerobic, and good clinical appraisal of the patient's clinical reaction when the antibiotic of choice was first used without cortisone.

It must be emphasized again that no patient was given "combined" therapy until she had had specific antibiotic therapy for at least two weeks. When cortisone was given, no other new variable was allowed. Thus each patient has acted as her own perfect control.

Repeated blood cultures were taken at this time. No positive blood cultures due to freed bacteria were ever found. No metastatic abscesses developed. There is no place in the regime for the use of "broad-spectrum" antibiotics and wishful thinking as to their possible specificity.

When adequate resolution has occurred, the cortisone dosage is reduced slowly by daily decrements and the antibiotic discontinued only after this is accomplished. Abrupt cessation could easily be fatal.

Results

Twenty cases of resistant gonorrheal cervicitis and recurrent salpingitis were completely cured. Ten of these have been followed over three to six years. In this group we have had 5 pregnancies, one of which, however, was ectopic. Some of these patients had been ill for a year or two; relief of pain in all was complete.

In all of these cases, the so-called "chronic cervicitis" which is really a subacute lesion cleared completely. We have had excellent results in the treatment of chronic endocervicitis in this manner. When deformity, tear, hypertrophy, or Nabothian cyst or scar formation had occurred, temporary remissions only could be obtained.

Twenty cases of postpartum, postabortal, or postcauterization pelvic cellulitis, with or without early tuboovarian abscess, all had complete remission. The amount of residual damage by scar depended directly on the duration of the disease before combined treatment.

Five cases of generalized peritonitis with bowel obstruction were successfully treated. There were no deaths.

Many patients developed complications of steroid therapy which faded as dosage diminished.

Conclusions

1. The combined use of cortisone and proved specific antibiotics will hasten cure in resistant pelvic infections.
2. The earlier this attack is used, the less will be the total tissue damage and result.
3. The more acute the lesion, as indicated by cervical discharge, tender granulation tissue, fever, leukocytosis, and elevated sedimentation time, the more immediate and permanent are the benefits of such treatment.

4. The lesions will not recur if therapy is adequate and early enough.
5. Resistant gonorrheal lesions and early tuboovarian abscess, single or bilateral, following pelvic cellulitis are best treated in this way as the treatment of choice.
6. Accessible abscesses should always be treated by early, adequate surgical drainage.
7. Once scar tissue has been laid down, the combined treatment is of no value.
8. We are at present starting to treat our patients much earlier in the course of their disease hoping to restore more normal pelvis.
9. Tuberculous infections must still be excluded until adequate animal experimentation has been done.
10. In this way we should be able to reduce the incidence of sterility and hysterectomy due to pelvic infection in our youngest and most fertile age group.
11. This series needs repetition and confirmation elsewhere under similar conditions before it can be considered a treatment of choice. Until that time it should be considered experimental and used only under the most careful supervision.

This series includes patients treated by myself and Dr. A. L. Richard, Dean and Professor of Obstetrics and Gynaecology, Dr. A. Nuyens, Assistant Professor of Obstetrics and Gynaecology, and Dr. J. Beggs of the Ottawa Civic Hospital. The initial research grant was made in 1949 by the University of Ottawa, with the supervision and support of Dr. Richard. Merck & Company, Inc., Schering Corporation, The Upjohn Company, Chas. Pfizer & Company, Inc., and Lederle Laboratories supplied the steroids and antibiotics used. Dr. Gibbons, Professor of Bacteriology, was most helpful. The Grey Nuns of the Cross of the Ottawa General Hospital gave complete and unselfish cooperation in the care and treatment of these patients.

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150 METCALFE STREET

Discussion

DR. ALBERT B. BROWN, Saskatoon, Sask.—I must admit that I have never used cortisone in the treatment of pelvic inflammatory diseases and indeed there are some who believe it to be contraindicated in the face of infection. However, from the literature it appears that cortisone, together with specific antibiotics, is being used more and more in the management of severe infections.

Theoretically it is not hard to find reasons for Dr. Hurtig's good results. Cortisone is known to have an anti-inflammatory effect, locally by minimizing or reducing the vascular and exudative response to infection, and systemically by a nonspecific antipyretic and antitoxic type of action.

It has been shown in tuberculous meningitis that cortisone potentiates the action of streptomycin and isoniazid hydrochloride by lysing or perhaps preventing the formation

of an exudate at the base of the brain with the result that cortisone has improved the survival rate in this disease. It seems reasonable to assume that a similar response to cortisone therapy would take place in the pelvis. It is also well known that cortisone therapy would be of value in the management of the very acute or catastrophic forms of illness. This is partly due to correcting the element of hypoadrenalism associated with such illnesses. Perhaps the debility which occurs with pelvic inflammatory disease is associated with a mild degree of hypoadrenalism and, if so, it might help to explain Dr. Hurtig's results.

From a theoretical point of view it seems that there may be a place for cortisone in the treatment of cases of pelvic inflammatory disease where there is an acute or exudative element present, and I think Dr. Hurtig's patients are of this type. There appears to be no evidence that cortisone has any effect upon scar tissue when it has formed and thus one could not picture its use in chronic inflammatory disease.

The use of cortisone in infections is not without danger. There is plenty of evidence that cortisone alone may increase the invasiveness of a wide variety of organisms and therefore it must be used together with a specific antibiotic in the treatment of an infective process. I would like to ask Dr. Hurtig how he determines the specific antibiotic when the infection is intra-abdominal.

One other word of warning is that cortisone masks the signs and symptoms of infection. Bowel perforation has gone undiagnosed in patients on cortisone because of this. A similar event might occur in the pelvis, that is, a tuboovarian abscess might rupture into the peritoneal cavity. This complication if unrecognized and not operated on early, results in a 50 per cent mortality rate.

Definite contraindications to cortisone therapy are borderline psychotic states and cardiac disease.

I think that Dr. Hurtig would agree that cortisone has no place in the treatment of early acute pelvic inflammatory disease and that there is no evidence to suggest that it is of value in the chronic cases where scarring has occurred. From Dr. Hurtig's results and from a theoretical point of view, cortisone would appear to be of value in a small group of severe cases which have received inadequate therapy and where an exudative process is going on, but only when the specific antibiotic is known and can be used along with cortisone.

HORMONE THERAPY AND THE Rh FACTOR*†

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SINCE the discovery, in 1939, of the Rh factor by Levine and Wiener, and their later demonstration of its relationship to hemolytic disease of the newborn, a continuous search has been made for therapeutic agents which might be of value in obstetrical Rh isoimmunization. A wide variety of agents have been used, the haptens of Carter, typhoid vaccine, and anhydrohydroxyprogesterone, to mention only a few. The early enthusiasm with which such drugs have been sponsored² has been matched only by the disappointment of other investigators who assessed their value.^{6, 8, 9} While techniques of prompt replacement transfusion of the liveborn infant have improved, overcoming almost all obstacles save hydrops and prematurity to date, no effective agent has been discovered for administration to the mother.

In this therapeutic vacuum, ACTH and cortisone held promise on both theoretical and practical grounds¹⁵: (1) Theoretically these hormones suppress antibody formation and act directly on the antigen-antibody complex. (2) Practically they are effective in the prevention and treatment of the hemolytic crises of congenital spherocytosis. It appeared to be reasonable that these same drugs might be effective in hemolytic disease due to the Rh factor, a similar process.

Two possible approaches to the use of hormone therapy in Rh-negative gravidas present themselves: (1) as prophylaxis to prevent sensitization; (2) as treatment during pregnancy where sensitization has already occurred in order to increase fetal salvage.

The Effectiveness of Cortisone on Sensitization Precipitated by Labor

On the grounds that prevention is the better part of cure, it is far better to prevent the occurrence of Rh sensitization in the first place, than to deal with its consequences. Progress has already been made in nonobstetrical immunization by proper blood procedures and the avoidance of intramuscular blood injections.

If the circumstances and mechanisms of obstetrical sensitization were better understood, it is possible that its incidence might be further reduced.

The purpose of this part of the investigation was to explore the factors involved in labor in the production of Rh sensitization. It is exceedingly rare for an individual to become sensitized during the first pregnancy unless a prior transfusion of Rh-positive blood has been given, for most persons require at least two injections of blood separated by an interval of a month

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before sensitization can be detected by the methods at our disposal,^{14, 20, 21} although obviously some change has occurred after the first injection which we cannot detect and which somehow makes this patient different from one who has never before received the antigen. About 5 per cent of women who are not sensitized at one delivery are found to be sensitized during their next pregnancy.^{4, 16} Whether this occurs as a result of the stimulus of blood from the second pregnancy or from the effect of labor in the preceding pregnancy is not known. It has been suggested that sensitization in the majority of cases is precipitated by labor itself,^{11, 12, 13} owing to the transfer in bulk of positive fetal red blood cells across the choriodecidual barrier, and Gainey and associates¹⁰ have shown that a disproportionate number of women sensitized to the Rh factor have had a history of induction of labor or traumatic delivery.

We present as evidence two series of Rh-negative women in labor: (1) a treatment series from the literature^{11, 13}; (2) a control series of our own.

In an effort to prevent the sensitization by labor, Hunter selected a group of 225 Rh-negative women who showed no antibodies at the time of delivery and gave to each a total of 1 Gm. of cortisone during labor and on the following 5 to 7 days. At 4 weeks post partum, he found only 1 sensitized.

In order to ascertain the exact incidence of sensitization, we ran a control or untreated series of 200 unselected Rh-negative white women from the public ward services of the Toronto General Hospital. None showed antibodies at the time of delivery when the blood serum was tested by the saline, albumin, trypsin, and indirect Coombs methods against selected Rh-positive and -negative cells.

Of the 200 Rh-negative women, 82 delivered Rh-negative babies, which corresponds closely with the theoretical distribution of the Rh-negative gene (40 per cent) in the male population. None of this group could have been sensitized to "D." The remaining 118 patients delivered Rh-positive babies. Of these women, 2 showed antibodies 6 weeks post partum.

In our control series, we found 2 cases of sensitization in 200 Rh-negative women. This series is being further enlarged to give greater validity to the incidence of sensitization. Meanwhile, we must conclude that routine use of cortisone in unselected cases is of little value.

It may be, however, that cortisone has value in certain specific instances, such as those previously referred to,¹⁰ where massive transfer of fetal blood may occur. In an effort to assess the risk of sensitization in this type of case, we are currently investigating labors complicated by third trimester bleeding, cesarean section, Pitocin stimulation, and a variety of traumatic obstetrical maneuvers in unsensitized Rh-negative women. In the meantime, we urge conservatism in the management of Rh-negative gravidas.

ACTH and Cortisone and the Sensitized Mother

The remainder of this paper deals with the therapeutic evaluation of these hormones in women who are already sensitized to the Rh factor. Hunter^{11, 12} reported a salvage of 10 infants from 12 such pregnancies and Christensen and associates,³ of 8 out of 10 with the use of ACTH or cortisone during pregnancy. DeCosta and co-workers,^{5, 6} reviewing the collective experience of reported small groups of cases as well as some of their own, felt that the outcome was not influenced by hormone therapy.

Our series includes those cases in our center which appeared to have the worst prognosis. It was hoped that if hormones were of outstanding value, only a few cases would be required to prove it. The number of patients of this type in any one center is not great and it was difficult to persuade them

to enter the hospital for prolonged treatment of unproved value. Only 15 such cases were collected over four years. They were chosen on the basis of history, titer and genotype of husband.

Investigation.—In addition to routine investigation, kidney function tests were done. Tuberculosis was excluded on the basis of chest x-rays and tuberculin tests. Rh antibody titers, gamma globulin determinations, eosinophil counts, and 17-ketosteroid level determinations were done at intervals throughout the course of therapy. Weight, blood pressure, and diet were carefully controlled on a regimen of salt restriction and potassium supplements.

Treatment.—Eleven of the patients were treated with ACTH* for from 10 to 75 days. A full therapeutic dose varying between 60 and 400 mg. daily by intramuscular injection was employed, depending upon the eosinophil response and ketosteroid levels obtained. Some difficulty in dosage was encountered when it was found that the potency of the drug varied considerably with the batches used. Our aim was not only to reduce the eosinophil count but to raise the 17-ketosteroid excretion levels to about double the pretreatment value. Higher doses seemed to be badly tolerated by the patients.

Four patients were treated with cortisone† for from 35 to 180 days on a dose of 100 mg. daily. This is comparable to the dose used in other reported series. Therapy was gradually reduced over a period of 3 to 5 days following delivery, no untoward complications being encountered at that stage.

Case Histories.—Short summaries of the treated cases are given. All patients were sensitized to the D antigen and in three instances this had apparently been caused by a mismatched transfusion. No cases of ABO incompatibility were encountered in this series.

Nine patients had had a history of stillbirth and 6 had had one or more neonatal deaths due to hemolytic disease. The antibody titer ranged from 1:32 to 1:4,096. All fathers were believed to be homozygous for D; in fact, all resulting babies were Rh positive and had strongly positive Coombs tests. Antibody titer is stated in terms of the albumin or blocking antibodies as this is considered to be the significant reading.

CASE 1.—Mrs. E. F., aged 25 years, gravida ii, para i, was admitted Nov. 27, 1951. There was a history of transfusion as a child. Her first baby, an erythroblastotic infant, had died at 13 hours. The albumin titer dropped from 1:32 to 1:2 while under observation. Treatment was commenced Dec. 1, 1951, with ACTH, a total of 1.6 Gm. being given intramuscularly over the next 16 days. Therapy was ineffective as measured by eosinophil and 17-ketosteroid level response. Spontaneous labor and delivery of a living erythroblastotic infant occurred three weeks before term. The infant weighed 6 pounds, had a hemoglobin of 12 Gm., and appeared clinically to be severely affected. It received multiple exchange transfusions and survived.

CASE 2.—Mrs. C. W., aged 27 years, gravida iii, para ii, was admitted Jan. 7, 1952. Her second child, an erythroblastotic infant, had died at 4 days in spite of exchange transfusions. Her albumin titer varied from 1:128 down to 1:4 while under treatment. ACTH was started Jan 13, 1952, and was continued for only 10 days when spontaneous labor supervened three weeks prior to term. She received a total of 3.7 Gm. of ACTH in doses up to 400 mg. daily. Eosinophil and 17-ketosteroid response seemed adequate. A 6 pound 8 ounce erythroblastotic infant was delivered spontaneously. Mildly affected, the child required only one transfusion and survived.

*ACTH was supplied for this investigation by the Armour Laboratories.

†Cortisone was supplied as Cortone acetate by Merck and Co., Limited.

CASE 3.—Mrs. C. W. (Case 2) again became pregnant and was admitted Jan. 24, 1954, for another trial of therapy. Antibodies were 1:32 on admission and dropped to 1:16. Treatment was commenced in the twenty-eighth week of pregnancy, Jan. 13, 1954, with ACTH gel, 40 units daily. She was delivered in the thirty-second week following spontaneous premature labor after receiving a total of 560 units of ACTH gel. The infant weighed 3 pounds 8 ounces, with a cord blood hemoglobin of 10 Gm. and died in less than 3 hours without transfusion. The patient became emotionally depressed under therapy, causing some difficulty in the management, but the depression cleared rapidly at the conclusion of treatment.

CASE 4.—Mrs. E. I., aged 28 years, gravida iii, para ii, was admitted April 21, 1952. Her second pregnancy 2 years earlier had produced a hydropic infant at 37 weeks. Her albumin titer remained stable at 1:64 while she was under observation. Treatment commenced April 26, 1952, in the thirtieth week and continued for 43 days. She received a total of 5 Gm. of ACTH and became markedly despondent as the dosage was increased to effective levels. She went into spontaneous labor at the thirty-sixth week, and delivered a 5 pound erythroblastotic infant spontaneously. The hemoglobin of the infant's cord blood was 14 Gm. per cent. The baby was transfused and survived.

CASE 5.—Mrs. M. K., aged 33 years, gravida viii, para vii, was admitted Feb. 16, 1953. Her first five pregnancies had been normal but the sixth infant was jaundiced at birth and survived with transfusions. The seventh pregnancy ended in a hydropic infant. She had a history of hysteria and depressions which showed a tendency to recur. While under treatment the patient became erratic and almost unmanageable. Titers varied from 1:64 to 1:4. Treatment was started Feb. 21, 1953, and continued for 28 days. She received a total of 2.5 Gm. ACTH gel, the average dosage being 100 mg. per day. The emotional disturbance became severe and almost necessitated discontinuation of therapy when spontaneous labor began in the thirty-fourth week. An intrapartum abruptio placentae occurred which was moderately severe and was followed by a postpartum hemorrhage. She was delivered of a 4 pound 4 ounce erythroblastotic child with a cord blood hemoglobin of 9.2 Gm. Clinically pale, with enlarged liver on delivery, the infant survived with repeated transfusions.

CASE 6.—Mrs. J. S., aged 27 years, gravida iii, para ii, was admitted April 1, 1953. She had been sensitized by abortion and transfusion in 1946. Her second pregnancy the following year resulted in a stillbirth; there was no autopsy. Her titer ranged from 1:32 to 1:16 under observation. Treatment was commenced April 8, 1953, in the twenty-fifth week of gestation and continued for 46 days. She received 2 Gm. ACTH and 2.5 Gm. ACTH gel. Spontaneous labor occurred in the thirty-sixth week and she was delivered spontaneously of a 6 pound 5 ounce erythroblastotic infant who was transfused and did well. A moderately severe postpartum hemorrhage occurred which was easily controlled.

CASE 7.—Mrs. M. E., aged 36 years, gravida iii, para ii, was admitted April 15, 1953. Her first baby was normal. The second, delivered at 37 weeks, was jaundiced and died in 4 days. Her titer varied from 1:32 to 1:8 under observation. Treatment was commenced April 21, 1953, in the twenty-ninth week of pregnancy and was continued for 35 days. She received a total of 2 Gm. ACTH gel, the average dose being 69 mg. per day. Labor and delivery occurred spontaneously in the thirty-fourth week. A 4 pound 13 ounce erythroblastotic child was delivered who was transfused and did well.

CASE 8.—Mrs. M. M., aged 33 years, gravida iii, para ii, was admitted June 23, 1953. Her first pregnancy was normal. The second child, delivered at 34 weeks, was erythroblastic, was transfused, and died at 36 hours. Her titer which was 1:16 rose under treatment from 1:256 to 1:512. Treatment with ACTH was started in the twenty-sixth week and continued for 30 days. There was felt to be an inadequate response to therapy as judged by 17-keto-steroid level and eosinophil counts. A total of 3.2 Gm. ACTH was given. Intrauterine death occurred in the thirtieth week, followed in a few days by spontaneous delivery of a macerated fetus that weighed 2 pounds.

CASE 9.—Mrs. J. W., aged 37 years, gravida vi, para ii, admitted Jan. 10, 1954, had had two normal full-term deliveries followed by three stillbirths occurring in the eighth,

seventh, and sixth months, respectively. Her titer varied over a wide range, being 1:256 on admission; it had been reported as 1:4,096. The level dropped eventually to 1:32 under observation. Treatment with ACTH gel was commenced Jan. 20, 1954, in the twenty-eighth week of pregnancy and continued for 28 days. Pregnancy was complicated by a degree of hydramnios which disturbed the patient. Labor occurred spontaneously in the thirty-second week and was complicated by a moderate abruptio placentae. A living hydropic infant weighing 5 pounds was delivered and survived for only 30 minutes.

CASE 10.—Mrs. A. K., aged 25 years, gravida v, para ii, was admitted May 31, 1954. This patient had been sensitized by transfusion and had no surviving children. There was a stillbirth at term with the first pregnancy, a neonatal death with the second, a spontaneous abortion early in the third, and a stillbirth at 8 months with the fourth pregnancy. Her titer rose while on treatment from 1:64 on admission to 1:512 before delivery. Treatment was commenced June 10, 1954, in the twenty-fifth week and was continued for 75 days on ACTH gel and later Duracton. A total of 3.6 Gm. of the drug was used. She was delivered spontaneously in the thirty-sixth week of a living, though seriously affected, erythroblastotic infant weighing 6 pounds 11 ounces that had a cord blood hemoglobin of 8 Gm. The infant was transfused promptly and survived. Throughout treatment the patient repeatedly showed signs of pre-eclampsia which never progressed to a serious stage.

CASE 11.—Mrs. A. B., aged 30 years, gravida iv, para ii, was admitted Jan. 16, 1955. This patient's first pregnancy ended in a full-term normal delivery but a stillbirth occurred at the thirty-seventh week in the second and a hydropic infant was born at the thirty-fourth week of the third pregnancy, during which she had received cortisone therapy. Her antibody titer remained constant at 1:64 throughout the period of observation. Treatment commenced January 20 in the twenty-first week of pregnancy and continued for 50 days during which she received 1.5 Gm. ACTH gel. The patient became emotionally disturbed under therapy as she had on a previous occasion. Intrauterine death occurred in the twenty-sixth week and she delivered a macerated fetus weighing 1 pound 6 ounces two weeks later, after a spontaneous labor.

CASE 12.—Mrs. T. T., aged 31 years, gravida iv, para i, was admitted Jan. 10, 1953. She had had one full-term delivery of a normal child, followed by a macerated stillborn infant at term and an erythroblastotic infant born at 28 weeks who died in the neonatal period. Her antibody titer was 1:8 and rose to 1:64 while on treatment. Treatment with cortisone, 100 mg. a day, was started Jan. 17, 1953, at the eleventh week of pregnancy and continued for 180 days. The patient was emotionally unstable and difficult to manage. Excessive weight gain and a rising blood pressure with albuminuria made it necessary to induce labor in this patient at the thirty-seventh week of pregnancy for toxemia. A living erythroblastotic infant was delivered spontaneously, was transfused and did well. Signs of pre-eclampsia subsided promptly and the patient's emotional disturbance improved.

CASE 13.—Mrs. A. B., aged 28 years, gravida iii, para ii, was admitted Jan. 10, 1953. Following a full-term delivery of a normal infant, this patient had had a macerated fetus at 37 weeks. The antibody titer at the start was 1:8 and rose while under treatment to 1:256. Treatment was commenced with cortisone, 100 mg. daily, in the twenty-fifth week of pregnancy and was continued for 60 days. The patient became confused and depressed after seven weeks of therapy and began to show signs of toxemia. Induction of labor was being considered when the patient solved the problem by going into labor spontaneously at 33 weeks. Intrapartum abruptio placentae occurred, with partial separation and moderate blood loss. A severely affected erythroblastotic infant who weighed 6 pounds 5 ounces was delivered spontaneously. Transfusions were given but the child died in 6 hours.

CASE 14.—Mrs. A. C., aged 34 years, gravida vi, para iii, was admitted March 9, 1953. This patient had three normal living children. A mismatched transfusion during the course of an operation for an acoustic neuroma in 1948 was apparently the cause of her sensitization. Following this her fourth and fifth pregnancies had ended in stillbirth. She was an obese and somewhat hirsute patient. Antibody levels were found to be 1:32 to 1:64 throughout the course of treatment. Cortisone was started in the twenty-first week of pregnancy on

March 16, 1953, and was maintained at 100 mg. daily for 90 days. The patient continued to gain weight excessively and finally began to show signs of pre-eclampsia in the thirty-third week of pregnancy. Intrauterine death was suspected one week later. After another few days labor began spontaneously and the patient delivered a macerated 5 pound 8 ounce fetus.

CASE 15.—Mrs. E. I., aged 39 years, gravida iv, para ii, was admitted April 1, 1953. This patient had been treated with ACTH the preceding year and had achieved a living child from her third pregnancy, the second having ended in a hydropic infant. Her titer was steady at 1:64. Treatment was started April 6, 1953, in the thirtieth week of pregnancy with cortisone 100 mg. daily, and continued for 35 days. A hydropic infant weighing 4 pounds 6 ounces was delivered following a spontaneous labor and low forceps delivery. The infant died in twenty minutes.

Comment

Potter describes stillbirth as the major unsolved problem in hemolytic disease due to the Rh factor. It causes a gross loss of 20 per cent of affected babies.^{1, 17} We have designated as a successful outcome all live births in our series. Thus we eliminate the variable effect of neonatal care. Techniques of caring for the newborn affected by hemolytic disease have improved so vastly that today it can almost be assumed that an erythroblastotic baby delivered alive will survive.

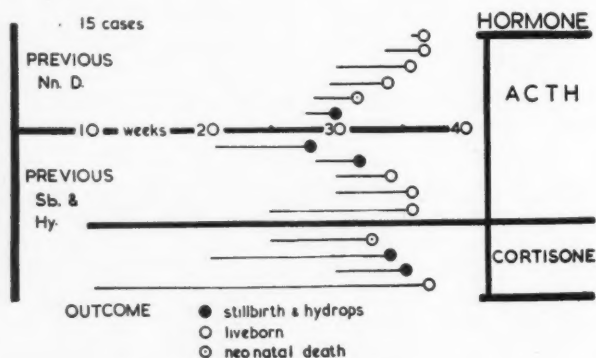


Fig. 1.—Duration of therapy.

The factors which increase or decrease the 20 per cent loss of affected babies are well known. We are indebted to Allen, Diamond, and Jones¹ for our knowledge of the natural history of the disease and in particular for the factors affecting the stillbirth rate. These are:

1. *History*.—The more serious the past history, the more ominous the outlook for stillbirth, but it is not true that once a stillbirth always a stillbirth.

2. *Titer*.—The effect of antibody titer and history is additive. High titers are associated with a high incidence of stillbirth. The effect of titer seems to be a resultant of antibody concentration and the duration of its action.

3. *Term of Gestation*.—Death in utero occurs at a relatively constant rate from the seventeenth week onward to term and some premature infants may have escaped this relentless process by delivery before it occurred.

4. *Paternal Genotype*.—This factor affects prognosis for a heterozygous father may contribute a negative gene producing an Rh-negative and hence unaffected child.

Although our series is made up of cases the prognosis of which was as bad as possible on the basis of history, titer and genotype, two factors favoring the salvage rate are apparent from Fig. 1:

First, only those pregnancies are included in which the child remained alive in utero long enough to receive treatment. Some deaths in utero occurring after the seventeenth week did not come to our attention in time and are not included. This fact increases the effect of selection in our series and applies equally to any treated group.

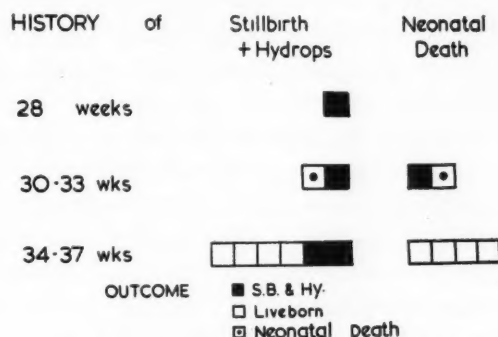


Fig. 2.—Early delivery and outcome.

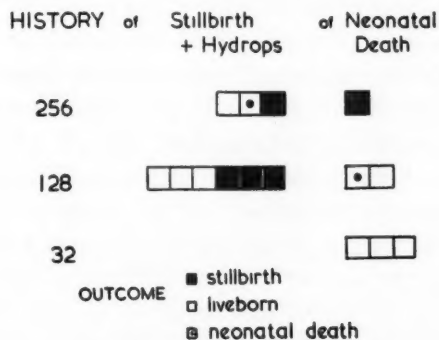


Fig. 3.—Titer and outcome.

Second, no pregnancy proceeded beyond the thirty-seventh week and our successes are all in the groups delivered from the thirty-fourth to the thirty-seventh week. In this group our salvage was 8 out of 10 cases. These 8 cases escaped the inevitable incidence of stillbirth in the latter weeks of pregnancy. Labor was surgically induced in one case, the onset of premature labor was spontaneous in the remaining 14. Thus the only clearly demonstrable effect of hormone therapy appears to be the two-edged weapon of premature delivery. It will be seen also that the length or type of therapy is not apparently related to the outcome. All the liveborn infants were erythroblastotic clinically, requiring repeated transfusions to achieve survival.

Fig. 2 demonstrates that our successes occurred in the period from 34 to 37 weeks and none survived under 33 weeks. In this latter group there were three deaths in utero and 2 liveborn infants who did not survive the double hazard of marked prematurity and severe Rh hemolytic disease.

Fig. 3 shows the additive effect of titer and history on the outcome. There were no losses in the low-titer range and even where the titer was 1:256 and higher there was a 50 per cent salvage. In addition to this there was one stillbirth and one neonatal death despite treatment even in the group who had no previous history of stillbirth. It is not difficult to explain the bad results. It is more difficult to say that these drugs did not exert some good effect. We believe that the outcome in our series would have been the same without treatment when due allowance is made for selection of the cases. That is to say, the pregnancies survived long enough to receive treatment and were then delivered early.

The side effects were of such a nature as to cause great concern in the management of each of these cases. These were of three types: (1) medical, (2) psychic, (3) obstetrical.

These drugs produced a clinical state akin to that of incipient toxemia with fluid retention and a tendency toward elevation of blood pressure. True toxemia developed in 2 cases; one of these patients became acutely depressed but recovered spontaneously after surgical interruption of the pregnancy at 37 weeks. Three others showed marked depression under treatment. There were 3 cases of intrapartum abruptio placentae, none being associated with defect in the clotting mechanism of the blood.

We are forced to conclude from the standpoint of treatment that these hormones exert no major effect in the prevention of stillbirth. The only minor effect noted in our series is that of premature induction of labor. Statistical study of a group this small and without controls is of course futile and we were unable either to acquire or to handle a large enough series of cases of this type for statistical evaluation. But in the light of our present knowledge any possible benefit to be derived from hormone therapy in hemolytic disease is more than outweighed by the hazards inherent in treatment. Further use of these drugs for this purpose is judged to be useless and may be dangerous.

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UTERINE HEMORRHAGE AND AFIBRINOGENEMIA*

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OF ALL the factors which cause uterine hemorrhage, either during pregnancy or labor or following delivery, afibrinogenemia is the one which, for less than a decade, has received the most attention.

This pathologic entity was suspected by DeLee⁶ in 1901. In 1949 the observations of Maloney, Egan, and Gorman¹ attracted attention when the latter detected marked fibrinolysis in the blood of patients with premature separation of the placenta and thus suggested that the afibrinogenemia was the result of this fibrinolysis. The physiologic processes have been carefully scrutinized and studied since and specific treatment has been undertaken.

To explain this disturbance in the mechanism of coagulation, it is necessary first to recall the basic processes of coagulation. In the formation of the clot three principal reactions occur.¹² The first is the preparation of thromboplastin liberated in the blood stream as the result of the reaction of blood platelets with a plasma factor, the thromboplastinogen. The second reaction is the conversion of prothrombin into thrombin assisted by thromboplastin. Here certain other factors also intervene, such as calcium ions, proconvertin and accelerin on the one hand, and heparin on the other, the equilibrium between which is necessary to maintain the integrity of the mechanism. The last stage is the formation of fibrin due to the reaction of thrombin with fibrinogen.

The etiology⁵ of the coagulation defect in afibrinogenemia has not been definitely established. Weiner's^{3, 4} seems the least popular of the three theories found in the literature. This theory supposes the production of toxic substances of placental or fetal origin which reduce the formation of fibrinogen in the maternal liver. Schneider's^{8, 13} hypothesis, the second theory, depends on the production of thromboplastin or of a related substance originating in the uterus and liberated in the maternal blood stream. The entire intravascular coagulation process would be triggered by such a mechanism, causing a reduction of fibrinogen. The third theory was proposed by the Smiths⁷ in 1945 when they discovered the presence of a fibrinolytic enzyme in gravid toxemic patients. Subsequently, other investigators observed such an enzyme present in states of shock and in certain cases of retention of a dead fetus.

This fibrinolytic or fibrinogenolytic enzyme is considered more and more frequently as being the sole cause of or at least partially responsible for the disappearance of fibrinogen.^{8, 9} This active substance, capable of hydrolyzing

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fibrinogen and fibrin, is called fibrinolysin. In order that this hydrolysis may occur, the latter substance requires conversion by a precursor enzyme, pro-fibrinolysin, which is normally present in plasma and is activated by other factors. Cytofibrinokinase is one of the activating agents. It is located in such tissues as the placenta, the decidua, the endometrium, as well as the myometrium. The catabolic and autolytic changes which occur in the cells of these tissues when a premature separation of the placenta takes place cause the production of intracellular cytofibrinokinase.

This hemorrhagic diathesis is especially associated with premature separation of the placenta, amniotic embolism, and "in utero" retention of a dead fetus. It may also occur during severe toxemia or secondary to the retention of placental fragments. Obstetrical shock and certain surgical interventions have been indicated in the past as trigger mechanisms in afibrinogenemia. This pathologic condition may even occur following normal delivery.

Should this syndrome be suspected whenever serious hemorrhage occurs, it is important that diagnosis be established as quickly as possible by performance of the necessary coagulation tests of the mother's blood. Treatment must then be undertaken in consideration of the two following requirements: (a) elimination of the source of the blood dyscrasia; (b) replacement of the elements necessary to coagulation while the lost blood is being replaced. The first may be met by various means depending upon the causal complication. Transfusions of plasma or whole blood and the administration of fibrinogen fulfill the second criterion.

The possibility that certain blood factors, such as accelerin and prothrombin, may be somewhat modified is gaining acceptance. The alterations in accelerin and prothrombin are, however, so slight that the afibrinogenemic condition remains the only important cause. The injection of fibrinogen is therefore the most direct means of re-establishing the mechanisms involved in coagulation. The amount of fibrinogen injected must be at least 4 Gm., and it is advantageous to alternate this treatment with transfusions. Should fibrinogen be unavailable, transfusions become more and more a requisite. Not only will transfusions include a certain amount of this principal factor (fibrinogen), but they will also correct a deficiency, however small it might be, of certain other elements, and they will restore the blood volume. Hysterectomy is necessary in those desperate cases which do not respond to this therapy, but it is not always successful.

The following are 4 cases of postpartum hemorrhage due to afibrinogenemia:

CASE 1.*—Mrs. L. C., had a normal confinement in 1951 and had aborted two years previously. On July 10, 1954, she had a normal full-term delivery. Labor was absolutely normal. On leaving the case room, the uterus was well retracted and bleeding was normal. One hour later bleeding had increased and one ampule of Ergotrate was given intramuscularly. Hemorrhage, however, continued and quickly assumed alarming proportions. The blood pressure dropped to 40/10 mm. Hg. The pulse became rapid, the patient was semi-conscious. Transfusion was begun before the patient was transferred to the operating room for a uterine examination which was found to be negative. A tamponade of the

*Cases 1 and 2 have already been published.²¹

uterus and vagina was performed but the packing became rapidly soaked and the hemorrhage continued. The pulse then became imperceptible and blood pressure negative. Energetic treatment by means of pressure transfusions and analeptics induced improvement permitting hysterectomy. Subsequent to the operation, clots were noticed in the vagina. The patient left the hospital fifteen days later, well on the road to recovery.

CASE 2.*—Mrs. D. L., on Oct. 8, 1954, had a normal full-term delivery. Three hours after delivery vaginal hemorrhage was observed, of such proportions as to require 500 c.c. of plasma with ergometrine. In spite of this treatment, the pulse became rapid and thready, and the blood pressure fell to 60/40. Whole blood transfusion under pressure was given because the hemorrhage persisted and the blood showed absolutely no tendency to clot. Uterine examination being negative, hysterectomy was deemed unavoidable. During last minute preparations for operation, it was suddenly noticed that the hemorrhage had diminished considerably. Another pressure transfusion, 1,000 c.c., was given in view of this encouraging situation. Soon afterward the patient recovered from her shock. Improvement from then on was constant and convalescence was normal.

CASE 3.—Mrs. R. L., 33 years old, was admitted at 1:30 P.M., Sept. 11, 1955, with a diagnosis of premature separation of the placenta and uterine hemorrhage in the eighth month of pregnancy. There were absolutely no signs of toxemia. Fetal auscultation was negative, the pulse rate 120 per minute, blood pressure normal. Her eight previous pregnancies had all been normal save one where symptoms of eclampsia had occurred. The membranes were ruptured at 7:00 P.M., but from this moment vaginal bleeding increased. Labor was induced therapeutically and contractions began normally a very short time afterward. The period of dilatation lasted but 30 minutes and a dead fetus was delivered. Following expulsion of the placenta, hemorrhage again increased and the situation became alarming. Examination of the uterus disclosed that there were no fragments of placenta retained, no cervical or vaginal tears. As transfusion was begun, ecchymosis was seen to be distributed over most of the patient's body, especially at the sites of subcutaneous injections. Hemorrhage diminished at the termination of transfusion. The discharge quickly became normal. The patient had received 500 c.c. of whole blood.

CASE 4.—On July 12, 1955, Mrs. M. R. was admitted to the hospital in severe shock subsequent to hemorrhage which occurred after an apparently normal confinement at home. On admission, the patient was bleeding abundantly and there were no signs of clotting. The semiconscious patient, the imperceptible pulse, and the blood pressure of zero presented a very poor outlook. The negative uterine examination was immediately followed by a tamponade of the uterus and vagina with very little apparent effect. Continuous blood transfusions under pressure had, however, improved the general state. Approximately 90 minutes after admission patient's pulse had become perceptible, the blood pressure was 80/40 mm. Hg. There was, however, little hope of controlling the hemorrhage so hysterectomy was performed. During the first six postoperative days we were confronted with the problem of a severe renal deficiency as shown by an almost complete anuria and azotemia which varied from 1.05 to 3.8 Gm. per cent. As diuresis began on the seventh day, our patient became increasingly incoherent with Cheyne-Stokes respiration. Death occurred in the terminal stages of uremia. Autopsy showed lower nephron nephrosis as well as a fairly extensive infarct of the anterior lobe of the pituitary as seen in Sheehan's syndrome. There was also a hemorrhagic infiltration of the incision and the retroperitoneal space.

Comment

Presentation of these 4 cases of hemorrhage due to a faulty coagulation mechanism emphasizes the importance of early diagnosis of this syndrome. In all of our patients, provisional diagnosis was generally made early enough, especially when facilitated by the presence of generalized ecchymosis or the lack of coagulation of the hemorrhagic discharge. In each case, a rapid but careful examination was performed to eliminate other possible causes of vaginal hemorrhage. The laboratory was called in immediately to confirm,

if possible, the suspicion of faulty coagulation. Several cubic centimeters of blood were taken for the purpose of observing the type of coagulation. In each instance we noticed a minute clot which dissolved immediately.

Once the diagnosis of afibrinogenemia was confirmed it remained necessary to determine whether there were a friable clot, exceedingly weak in fibrinogen, or whether fibrinolysis had occurred. In order to demonstrate positively the presence of a substance which causes definite lysis, one must perform the test which has been called the "fibrinolytic activity test." A series of mixtures, which include normal plasma and patient's plasma, is prepared. Following recalcification, these mixtures are placed in an incubator at 37° C. Normally in such a mixture clot lysis should not occur before 24 to 36 hours. These tests were performed in 3 of the 4 cases studied. In Cases 1 (Table I) and 2 (Table II) lysis occurred within 16 hours. In Case 4 the clots were liquefied after 24 hours (Table III). In the third case these tests were not performed, but spontaneous lysis occurred so rapidly that we necessarily thought of a very active substance causing lysis.

TABLE I. FIBRINOLYTIC ACTIVITY TEST (CASE 1)

TUBE	PATIENT'S PLASMA (C.C.)	NORMAL PLASMA (C.C.)	RESULTS
1	0.4	0.1	Complete lysis after 16 hours
2	0	0.1	No lysis after 48 hours
3	0.1	0.2	Complete lysis after 22 hours
4	0	0.2	No lysis after 48 hours
5	0.1	0.3	Complete lysis after 48 hours
6	0	0.3	No lysis
7	0	0.4	No lysis

TABLE II. FIBRINOLYTIC ACTIVITY TEST (CASE 2)

TUBE	PATIENT'S PLASMA (C.C.)	NORMAL PLASMA (C.C.)	RESULTS
1	0.2	0	Complete lysis after 16 hours
2	0.15	0.35	Partial lysis after 24 hours
3	0.1	0.1	Complete lysis after 6 hours
4	0.05	0.45	Lysis not very clear
5	0	0.2	No lysis

TABLE III. FIBRINOLYTIC ACTIVITY TEST (CASE 3)

TUBE	PATIENT'S PLASMA (C.C.)	NORMAL PLASMA (C.C.)	RESULTS
1	0.02	0.18	Complete lysis after 72 hours
2	0.18	0.02	Complete lysis after 24 hours
3	0.1	0.1	Complete lysis after 30 hours
4	0	0.2	No lysis
5	0.2	0	Complete lysis after 12 hours
6	0.15	0.05	Complete lysis after 48 hours
7	0.05	0.15	Complete lysis after 24 hours

Normally, our hematologist makes rapid tests for the presence or complete absence of fibrinogen in the specimen obtained. Several units of thrombin are added to 1 c.c. of blood. Lack of clot, therefore, indicates complete disappearance of fibrinogen. The cases studied, namely Cases 1, 2, and 4, showed that the coagulation time was prolonged rather than that there was an absence of clot formation.

If we seem to prefer the theory of lysis, it is because we have demonstrated some lysis in 3 cases plus the fact that it appears to us to be the most acceptable in the majority of cases. Looking upon afibrinogenemia as a result of a massive depletion, it is difficult to conceive how the organism is able

to survive the multiple thromboses which this total depletion of fibrinogen would cause, especially when it is so definitely sensitive to the slightest vascular obstruction.

We wish to emphasize that in 3 out of 4 cases the hemorrhagic phenomenon occurred in patients in whom a normal pregnancy had been terminated by an equally normal parturition.

Once the deficiency of fibrinogen has been demonstrated as the etiological factor, treatment theoretically appears simple enough. Actually, intravenous administration of 4 Gm. of human fibrinogen^{4, 5} usually suffices to repair a condition of hypofibrinogenemia if the fibrinolytic substance is not excessive. In our immediate surroundings we were unable to depend upon a supply of this factor which quite often would have simplified the therapeutic problem. Consequently, the use of transfusions of whole blood or plasma has a double purpose. While these substances remedy the blood loss and militate against collapse, we can only hope that the amount of fibrinogen contained will be sufficient to restore the coagulation mechanism.

The injection of 500 c.c. of blood in our patients and the injection of the same quantity of plasma, as well as 800 c.c. of blood in another, were sufficient to stop hemorrhage. In view of the fact that 500 c.c. of blood contains approximately 500 mg. of fibrinogen, we must conclude that this small quantity was sufficient to increase the titer of fibrinogen in the blood stream at least to the minimal level compatible with hemostasis. In one patient there was no response to transfusion and a hysterectomy became necessary as a life-saving measure. In the other case, removal of the uterus had caused hemorrhage to cease, but the patient died as a result of the complications of shock.

Summary

We have presented 4 cases of uterine hemorrhage. In at least 3 cases where hemorrhage occurred after a normal delivery we were able to demonstrate by laboratory methods a hypofibrinogenemia with a more or less marked fibrinolytic activity. Hemorrhage was checked in 2 patients by the use of transfusions alone. Hysterectomy was required in the other 2, one of whom died as the result of the complications of shock through blood loss.

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Discussion

DR. R. A. H. KINCH, Toronto, Ont.—Dr. Duchaine has presented 4 cases, 3 following normal labor characterized by severe postpartum hemorrhage one to three hours after delivery, and the last following severe abruptio placentae. He finds evidence of a severe lytic process in the blood of all these patients and naturally favors the fibrinolysin theory of the production of afibrinogenemia. We must interject here that Margulis in his study of fibrinolysis following normal delivery, unaccompanied by severe hemorrhage, found definite evidence of fibrinolytic activity of the blood within the first twenty-four hours post partum in 14 out of 20 cases. He attributes this to a stress reaction during labor.

The alternative theory to active fibrinolytic destruction of fibrinogen is that characterized by straightforward fibrinogen depletion through liberation of thromboplastin from damaged placenta into the circulating blood. This acts as a trigger factor activating the blood-clotting mechanism and multiple microscopic fibrin emboli or plugs are produced as a result, using up all or nearly all the available circulating fibrinogen. Following this intravascular coagulation, the second phase of the reaction is an incoagulable state of the blood.

Those who oppose this theory feel it cannot account for the rapid removal of the majority of these fibrin plugs. Recently it has come to light that a tissue extract, cytofibrinokinase, the purpose of which is to start off the fibrinolytic system in the plasma, is present in very high concentration in the myometrium. The essayist feels that it is liberation of this substance which produces active hydrolysis of the fibrinogen, causing it to disappear.

I, myself, retaining the British faculty for compromise, prefer to believe that the two systems are complementary. Initially, thromboplastin is liberated and produces intravascular coagulation. Intravascular coagulation then activates plasma profibrinolysin to liberate fibrinolysin in order to digest the excessive fibrin and act as a protective mechanism, keeping the blood fluid. If this becomes excessive, this mechanism protects against one situation only to subject the woman to the other.

You will say, during the heat and sweat of dealing with these catastrophic cases, does it really matter what the etiology is? Well, calm reflection will show that if a rapid method were available to differentiate the cases associated with lysis from those without, it might have considerable therapeutic significance.

If the situation is a pure fibrinogen depletion with no excessive fibrinolysis, then the cure is replacement with fresh blood and/or fibrinogen. The fact that recovery occurs in a very high proportion of reported cases with this management supports the absence of fibrinolysis. In these cases, hysterectomy may be dangerous. It subjects the patient to major surgery, the only result of which is to transfer the bleeding point to a possibly more inaccessible place. If, however, the real trouble lies in the myometrium, i.e., the cytofibrinokinase, then hysterectomy is the logical treatment and explains the exceptional case in which this operation stops the bleeding.

The crux is speedy differentiation and this we have not yet attained. Determination of fibrinolysis takes time. The "Fibrindex test" or thrombin time, as Dr. Duchaine terms it, is a reliable test, provided it is carried out under standard conditions, for detecting the presence of afibrinogenemia. In 50 cases, we have found that a prolongation of the clot formation time over ten seconds means either actual or potential coagulation defect. This does not dictate our treatment but it warns us of trouble and should make us look around for supplies of fresh blood and fibrinogen, in order to replace the coagulation system.

In closing, I would like to enlarge or remark on one sentence of Dr. Duchaine's paper. He states in the case report of severe abruptio: "There was complete absence of toxemia of pregnancy." Yet, this case was associated with a coagulation defect. This points again to the therapeutic advantage of classifying cases of abruptio placentae into those with blood which will clot or which will not clot, rather than into cases with or without toxemia.

THE MEASURING LINE*

The Decline in Maternal Mortality in Canada and Reasons Therefor

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"And I lifted up mine eyes again, and looked, and behold a man with a measuring line in his hand."¹

ONE of the duties of a national Society such as ours is to use a measuring line to determine what has been accomplished and to compute the time and labor it may cost to achieve even more. For our Society the *basic* measuring line is maternal mortality. The purpose of this paper is to discuss the decline in maternal mortality and the reasons therefor, especially in Manitoba.

There is no need to stress the importance of making every effort to reduce the number of deaths of women in their most sacred function. Nor need one remind this historically minded audience of the terrific toll of mothers from puerperal fever in the early nineteenth century. It took at least fifty years to convince physicians of the contagiousness of puerperal fever. After that idea was accepted, the belief was still held that a certain inevitable risk attended on childbirth. That great obstetric teacher, J. B. DeLee, coined the phrase: "Parturiens, ipso facto, in mortis periculo est," and the other maxims in bronze on the walls of the delivery rooms of the old Chicago Lying-in Hospital, "Non vi, sed arte" and "Primum non nocere," emphasized the dangers of childbirth and the need for gentleness.

At the close of World War I the medical world began to ask whether all maternal deaths were a biologic necessity. This awakening of the obstetric conscience occurred everywhere in the civilized world at about the same time. In Britain the Maternity and Child Welfare Act of 1918² marked the official entrance of Public Health Authorities into the realm of maternal welfare. In 1919 by act of Parliament a Dominion Council of Health was created and the first meeting of the Council was held in Ottawa Oct. 7 to 9, 1919.³ Dr. Helen MacMurchy was appointed by the Dominion Government as chief of the division of child welfare. In 1929, under Dr. Ray Lyman Wilbur in the United States, a Committee on Child Health and Protection was formed with the strong personal endorsement of President Hoover, and in the next year a White House Conference was held. The Royal College of Obstetricians and Gynaecologists was created in Britain in September, 1929. The Royal College of Physicians and Surgeons of Canada came into being in 1930, and in the same year the American Board of Obstetrics and Gynecology was formed. In 1927 the Manitoba Government set up a separate ministry of Health and Public Welfare

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with the late Dr. E. W. Montgomery as Minister. The first problem he tackled was maternal mortality. An enquiry form was mailed to each doctor who signed a death certificate for a pregnant woman. This practice continues. In February, 1928, Dr. Helen MacMurchy's⁴ report, "Maternal Mortality in Canada," appeared. The period she chose for study was July 1, 1925, to July 1, 1926. There were 237,199 births in that period and 1,532 maternal deaths, a rate of 6.4 per 1,000 live births. By provinces Manitoba had the highest rate, 7.7.

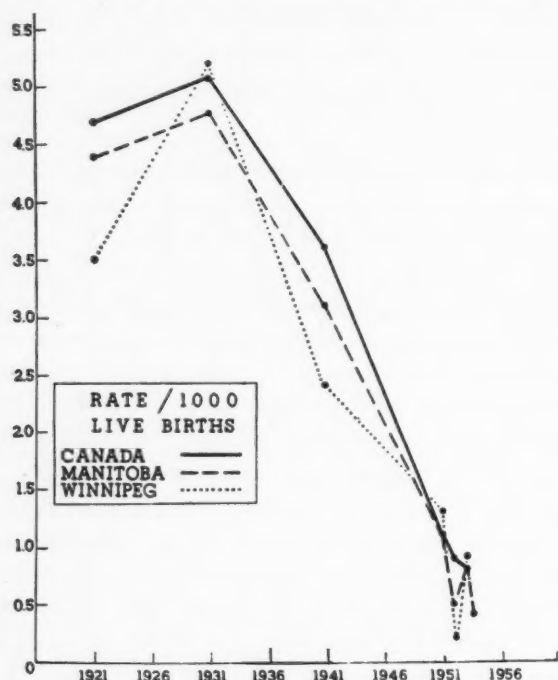


Fig. 1.—Decline in maternal mortality in Canada, Manitoba, and Winnipeg, 1921-1954.

Following the appearance of the report the Canadian Medical Association set up a Maternal Welfare Committee and Manitoba and other provinces did likewise. In 1934, F. W. Jackson, then Deputy Minister of Health for Manitoba, R. D. Defries, and A. H. Sellers⁵ published "A Five Year Survey of Maternal Mortality in Manitoba, 1928-1932," and in the same year Phair and Sellers⁶ published "A Study of Maternal Deaths in the Province of Ontario." In 1940 Jackson, Rawson, and Couture⁷ published "Maternal Mortality in Manitoba, 1933-37, Second Five Year Period." It became evident in Canada that information regarding age, race, economic status, and medical care during pregnancy, labor, and the puerperium had to be sought. Manitoba was chosen for the test and the time was the two years between May 1, 1938, and April 30, 1940. The survey was made possible by grants from the Rockefeller Foundation, The College of Physicians and Surgeons of Manitoba, and the Canadian Medical Association. The Federal Department of Health lent Dr. Parks and Mme. Chasse to collate and codify the pregnancy, delivery, and maternal death forms, and the Manitoba Department of Health supervised the

project. Manitoba doctors did their part by filling out the detailed forms to the extent of almost 90 per cent. In the two years 27,965 births were recorded, at 23,422 of which there had been a doctor in attendance. Maternal deaths were 122. Of these, 89 were assigned to puerperal causes and 33 to associated conditions. This gave a maternal death rate of 3.26 per 1,000 live births, a rate less than half of that recorded in 1925-1926.⁸

Fig. 1 shows the comparative maternal mortality rates for Canada, Manitoba, and Winnipeg from 1921 to 1951 by five-year periods and from 1951 to 1954 by years. It will be seen that the rates of the three areas almost coincide. Between 1931 and 1951 there was a precipitous drop to one-tenth of the previous mortality.

In January, 1921, the Winnipeg General Hospital opened a prenatal clinic, one of the first in Canada. Results were at once apparent. In the period 1921 to 1928 not a single case of eclampsia developed in patients who had regularly attended the clinic.¹¹ On May 6, 1950, during the height of a Red River flood, the Maternity Pavilion of the Winnipeg General Hospital was opened. This is a five-story building, a block away from the main buildings, and embodying the latest ideas in maternity hospital construction and equipment. It is the main teaching center of the Department of Obstetrics of Manitoba University. The other obstetric teaching hospital, St. Boniface, last year opened a large new wing which contains a thoroughly modern maternity unit. Grace Hospital, Winnipeg, will erect a separate maternity unit in a year.

The reduction in maternal deaths in Canada from 1,257 in 1931 to 324 in 1953, and in rate from 5.1 to 0.8 is no mean achievement. The reduction is not peculiar to Canada but has occurred throughout the civilized world. Rosenfield¹⁰ wrote that in 1951 two states, Connecticut and Oregon, reduced their rates to a new low of 0.1 per 1,000 live births.

How were these reductions brought about? One may list general and specific reasons. The general reasons are:

1. Increased interest, both medical and lay.
2. Firm action by Public Health authorities.
3. Better teaching. Some universities have whole-time professoriates in obstetrics and gynecology.
4. Creation of higher qualifications through the Royal Colleges, the American College of Surgeons, the American Board and Obstetrical Societies.
5. Increased hospitalization and separate maternity hospitals.
6. Increasing emphasis on antenatal care.
7. Better nutrition. With this one associates the names of Dugald Baird¹² and Ebbs, Tisdall, and Scott.¹³
8. Improved anesthesia and analgesia.
9. Better understanding of the psychology of labor. We owe a debt to Grantly Dick Read.¹⁴ The emphasis of today is placed on natural labor rather than on twilight sleep.
10. Rural health nurses, health units, and diagnostic centers.^{4, 7}
11. Better cooperation within the profession.
12. Decline in tuberculosis, especially in young females.^{6, 18, 19}
13. Better treatment of associated conditions, notably cardiac disease, diabetes, and poliomyelitis.

In addition to these general reasons one may list measures directed specifically against the causes of puerperal death.

Puerperal Sepsis.—Prior to 1936 puerperal sepsis was the leading cause of maternal death. Septicemia accounted for 40 per cent of all maternal deaths in Manitoba in the five years, 1928 to 1932.⁵ Johnstone⁹ stated, "As late as 1936 the prevention of sepsis seemed to be the highest good the obstetrician could ever hope to attain." The researches of Lancefield and Hare,²⁰ Griffith,²¹ and the Colebrooks²² established Group A of the hemolytic streptococcus group as the chief infective agent. The idea of droplet infection was accepted. From 1938 the sulfonamides were in general use and about six years later penicillin, the first and greatest of the many antibiotics, became available. The barrier technique of nursing and prompt isolation of infected patients put an end to outbreaks of sepsis which as late as 1933 caused medical authorities to regard delivery in homes as safer than in hospitals.¹⁶ By 1940 puerperal sepsis as a cause of death in Manitoba had fallen to fourth place and the decline continues. The universal use of antibiotics has revolutionized the treatment of criminal and self-induced abortions, formerly a leading cause of death.

Hemorrhage.—The decline in deaths from hemorrhage has been much less acute. Practice has lagged behind knowledge for the value of blood transfusion was well known by 1920. At first the difficulty in civil practice lay in not having blood on hand for emergencies. Hospitals set up blood banks, then the Canadian Red Cross started its beneficent plan of supplying grouped and matched blood. World War II showed the value of plasma and plasma derivatives and substitutes, though fresh whole blood still ranks first. Reid¹⁷ and others have pointed out that such obstetrical crises as abruptio placentae, amniotic fluid embolism, and delivery of a dead fetus might produce afibrinogenemia. Happily, fibrinogen is now commercially available, and should be on hand in every maternity hospital. The third stage of labor is now better managed. Use of the comparatively new and reliable ergometrine has become standard. My personal practice is to have 0.25 mg. ergometrine or methyl-ergobasine injected intravenously immediately after the birth of the head, and to deliver the placenta, unless spontaneously expelled, by the Brandt-Andrews method of traction on the cord.¹⁵ If the placenta has not separated after twenty minutes it should be removed manually under deep anesthesia.

Toxemia and Eclampsia.—Improved antenatal care, better nutrition, avoidance of anemia, and the use of hypotensive drugs reduce the incidence and severity of toxemia. Patients who fail to respond to office treatment should be admitted to the hospital. If they do not improve with rest, sedative and hypotensive drugs, labor should be induced. The stronger hypotensive drugs should be used only in the hospital where the patient can be under close supervision. The obstetrical department of the Winnipeg General Hospital has recently agreed on the use of rectal Avertin (tribromoethanol) in cases of eclampsia.

Thrombophlebitis and Pulmonary Embolism.—Early rising and ambulation have reduced the incidence of thrombophlebitis. When it does occur we have anticoagulant drugs, lumbar sympathetic block, and/or ligation of the vein above the clot.

Cesarean Section.—Greatly improved anesthesia, the lower segment operation, and the availability of blood for transfusion have made cesarean section relatively so safe that it has almost displaced other operations for delivery except low forceps. High forceps and internal version are now of only historical interest. Radiology, in conjunction with clinical judgment, is of great assistance in assessing disproportion and disclosing possible fetal abnormalities.

Associated Conditions.—The most frequently met associated conditions are heart disease, tuberculosis, diabetes, and poliomyelitis. The incidence of tuberculosis has declined spectacularly. There is increasing recognition of the value of consultation and close cooperation of the obstetrician with the cardiologist, internist, biochemist, and surgeon. The value of cardiac surgery, even during pregnancy, has been clearly shown.

Summary

1. The decline in maternal mortality in Canada, Manitoba, and Winnipeg since 1931 has been demonstrated with statistics.
2. Reasons, both general and specific, for the decline have been set forth.
3. The need for cooperation within the profession is pointed out.
4. There is reason to hope that still further reduction in maternal deaths can be achieved.

I wish to thank Dr. G. J. Wherrett, Executive Secretary of the Canadian Tuberculosis Association, for information on mortality from tuberculosis, Mr. E. Singleton, Secretary of the Health Department of Winnipeg, and Mr. E. S. MacInnes, Recorder of Vital Statistics, Manitoba Government, for their kindness in supplying statistics and information regarding the Pregnancy Survey in Manitoba, and my colleagues in the Department of Obstetrics and Gynecology, University of Manitoba, for their help and encouragement.

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OXYTOCIN, NEWER KNOWLEDGE AND PRESENT CLINICAL USAGE*

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HORMONES of the posterior pituitary are employed extensively in the field of obstetrics. Their use was introduced by Blair Bell¹ in 1909 and Foges and Hofstätter² in 1910 to effect contraction of the uterus in postpartum hemorrhage caused by atony. Then, Hofbauer³ in 1911 used posterior pituitary extracts for the induction and stimulation of labor. Thereafter, a flood of papers on this subject appeared.

The number of papers which have been written on this subject since 1910 is quite large. Herzig,⁴ in his 1949 review, has given references to 155 papers which have appeared in the American literature alone. An equal or greater number have probably appeared in the European literature.

As might be expected just on the basis of the number of papers which have been written on the subject, the use of posterior pituitary before delivery has had enthusiastic advocates and just as outspoken critics. In the early days of its use (1914) Druskin⁵ wrote in the *American Journal of Obstetrics*: "Since the introduction of the antiseptic method by Semmelweiss and Oliver Wendell Holmes in the early forties, nothing has had such a far reaching effect on the practice of midwifery as the use of pituitary extract." This was certainly high praise for he was an enthusiastic user. A year later Quigley⁶ cited a then-current advertisement which stated, "Throw away your forceps and use pituitrin." Such unbounded enthusiasm was the product of the mind not only of an advertising copy writer, for Ross,⁷ writing in the *Zentralblatt für Gynäkologie* in 1911 compared pituitary extract to the employment of forceps.

However, as with any new therapeutic agent, there are dangers in employing this preparation, and these hazards were quickly pointed out. There were those who decried the use of this agent during labor except in very circumscribed instances, and they probably had adequate justification. Williams,⁸ the outstanding teacher and investigator in the field of obstetrics in this country during the first third of the present century, strongly condemned its antepartum employment by injection.

Some of the hazards, however, which were present then have been removed by developments in other fields. For example, the administration of posterior pituitary extract to patients who have borderline pelvis measured

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only by clinical means can be fraught with danger. Today some of the inadequacies in estimating pelvic capacity have been removed by the developments in x-ray pelvimetry although there are times and instances in which even this technique fails and actually misleads us. Practical experience has also given us information on the type of patient in whom labor might be easily induced. Today the risk of rupture of the uterus should be no greater theoretically in patients who receive pituitary extracts than during normal labor. We also know more about the resuscitation of the newborn, albeit perhaps not enough. Not only have we learned, however, but the chemists and physiologists have improved the products we use to such an extent that we have more consistent and reproducible material with which to work.

Historical

Perhaps a rapid recapitulation of the important landmarks in this history will be of interest. In 1895 Oliver and Schäfer⁹ first reported the pressor activity of extracts of the posterior pituitary gland. Not until 11 years later in 1906 was the oxytocic activity of this gland extract reported by Dale¹⁰ and then only as a note in a paper dealing with new pharmacological activity of ergot. Dale who was then working for a British pharmaceutical house, induced Blair Bell to try this extract in the human being. Bell¹ reported his findings in 1909 in a paper entitled "The Pituitary Body and Therapeutic Value of the Infundibula Extract in Shock, Uterine Atony and Intestinal Paresis." In the same year Dale¹¹ also reported on "The Action of Extracts of the Pituitary Body." One year thereafter, in 1910, appeared the paper by Foges and Hofstätter,² already alluded to, which described the use of pituitary extract in postpartum hemorrhage.

The first of what became a veritable deluge of papers on this subject was that by Hofbauer³ which appeared in 1911 describing the use of posterior pituitary extract for the induction and stimulation of labor. The many papers which followed discussed the pros and cons of pituitary extract in terms of the practice of the day. As we have already said, there were ardent proponents of its use, and those who thought it should not be employed. This latter group were undoubtedly influenced in their disapproval by personal experience with ruptured uteri or reports of this catastrophic accident.

In the early use the preparations were administered either subcutaneously or intramuscularly. This state of affairs, as a matter of fact, continues. The amount used as reported in the early papers was usually 1 c.c. or 15 minims. This amount of solution represented between 0.1 to 0.2 Gm. of the fresh gland, depending upon the manufacturer. There was no adequate assay of the actual potency of these early preparations. Thus the dosage was expressed in terms of volume in minims. Even though different preparations of the extracts did have varying potencies, it was observed fairly early that a dose of 15 minims given either intramuscularly or subcutaneously was generally much too large, resulting in many instances in tumultuous labor. In some cases tetanic contractions or, particularly in the grand multipara, rupture of the uterus resulted. These observations led to a reduction in the amount given to somewhere around 2 to 3 minims as the initial doses,¹²⁻¹⁷ with various time schedules adopted for the repetition of the doses as a function of the resulting labor. Many such methods were described. One of the more popular in this country was the regimen described by Watson¹⁸ in 1922.

That the method of administration of the hormone preparation was not generally considered satisfactory is reflected in the fact that Hofbauer,¹⁹ who

had used the drug early, reported with two collaborators in 1927 another technique for administering the drug which provided a somewhat better control of the rate of administration. They first tried sublingual administration (oral administration had been found essentially ineffective in 1910). Though there was some indication of success by this sublingual route, the results were not sufficiently consistent to be a reliable method for the induction or stimulation of labor. Thereafter they tried nasal application, with a cotton pledget soaked with the drug (20 minims) applied to the inferior nasal turbinate. The technique of this method was relatively simple, effective, and allowed effective control. The pledget could be removed or replaced as desired. This method had some vogue, but the more popular intramuscular and subcutaneous routes generally persisted, partly because of ease of administration. It should be pointed out that these investigators recommended accurate positioning of the pledget in contact with the mucous membrane of the inferior turbinate. Many who subsequently tried the method merely plugged one or the other of the nares with the cotton, which is an ineffectual method.

As time passed there seemed to be an increasing acceptance of the use of the hormone in academic circles. As witness to this, two papers may be cited. Eastman,²⁰ in a paper read before the American Association of Obstetricians and Gynecologists in September of 1946 described the experience with the use of the drug at The Johns Hopkins Hospital. From 1926 to 1935 the hormone was administered intranasally. From 1935 to 1940 no posterior pituitary hormone was employed before the delivery of the baby. From 1940 to 1945 the hormone when it was used was given in doses of $\frac{1}{2}$ to 1 minim intramuscularly. It is our impression from this paper that Eastman was in favor of the use of this hormone preparation if it was *used properly*. On the other hand, we have seen a paper which cites this same talk stating that Eastman was not in favor of the use of posterior pituitary before delivery.

Another important paper at this time was read by Duncan Reid²¹ of the Boston Lying-in Hospital before the Boston Obstetrical Society in November of 1945 and published in 1946. In this paper Reid reviewed the experience with the drug during the years 1940-1945 at the Boston Lying-in Hospital. During this period the hormone was given intramuscularly to all patients who had uterine inertia with no cephalopelvic disproportion—a total of 1,609 patients. The starting dose was 1 minim, but—and this is an important part of this contribution—the dosage was increased until the patient had *effective uterine contractions*. Thus to achieve the desired result doses up to 15 minims were given. Reid approved of the use of the drug, citing that it is unfair to condemn a drug *because it is misused*. We are completely in accord with this view. Obviously many drugs in our therapeutic armamentarium are dangerous to life and limb if improperly used.

The intramuscular, subcutaneous, or intranasal administration of this drug prior to the delivery of the baby all have their disadvantages in the lack of fine control. One might postulate that the intravenous administration of the hormone should be the ideal way, since by this method extremely small amounts of the drug can be introduced into the circulation at one time and the concentration of the hormone in the infusion fluid can easily be changed. Though intravenous drip therapy had been in use for many years for other purposes, the first mention of the use of this technique for the administration of Pitocin for induction and stimulation of labor which we have been able to find is a paragraph in a paper published in 1943, entitled "Response of Human Pregnant Uterus to Pitocin Tannate in Oil" by Page.²² Herein he states,

"The most physiologic responses in severe primary uterine inertia have actually been obtained by giving an intravenous infusion of normal saline containing 10 to 20 units of pitocin to the liter. By constant observation and controlling the number of drops per minute, the obstetrician may control the character and amplitude of contractions adequately. The latter technic deserves further trial in selected cases of marked uterine inertia."

The results of other trials of this technique appeared in 1948 by Theobald and his associates,²³ by Jeffcoate²⁴ in England, and by Hellman^{25, 26} in this country. Since these publications there have been many other papers, all essentially confirming the usefulness of the hormone with this technique when properly employed.

Chemistry and Physiology of Preparations

Until now we have used the word Pitocin, the proprietary name of the preparation marketed by Parke, Davis & Company to describe the material we have used. It is a partially purified preparation containing more of the oxytocic activity of posterior pituitary than the pressor activity. Or, if you will, the pressor principle—vasopressin—has been largely but not completely removed. This partial purification of the active posterior pituitary principles was achieved by Kamm and his associates²⁷ in 1928. Before that most of the preparations in clinical use were essentially extracts containing all the activities of the posterior pituitary such as we associate with the proprietary name of "Pituitrin." Kamm's work in 1928 made available that preparation containing largely oxytocic activity known as "Pitocin" and that preparation containing largely pressor or antidiuretic activity known better as "Pitressin." Neither of these products is pure, each being somewhat contaminated with the other activity. Pitocin, for instance, contains, besides oxytocic activity, about 5 per cent of pressor activity.

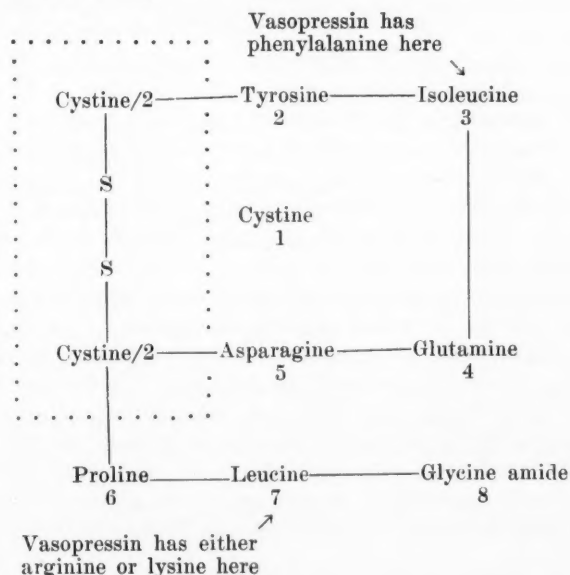


Fig. 1.—Schematic representation of amino acid structure of oxytocin and vasopressin. The structure of oxytocin is shown.

Our interest in the hormones of the posterior pituitary has increased recently by our association with Dr. Vincent du Vigneaud who is Professor of Biochemistry at Cornell University Medical College. He²⁸ and his associates

over the years have been active in characterizing and purifying the active principles of this gland. In recent years they have succeeded in isolating and determining the structure of oxytocin,²⁹⁻³² the substance largely responsible for the oxytocic activity, and vasopressin,³³⁻³⁵ the substance largely responsible for the pressor antidiuretic activity. In addition they have succeeded in synthesizing both oxytocin^{31, 36} and vasopressin.^{37, 38} Oxytocin has the structure shown diagrammatically in Fig. 1. It is a polypeptide composed of eight amino acids and three molecules of ammonia. Vasopressin has a structure much like oxytocin, except that vasopressin contains phenylalanine in place of isoleucine, and either arginine if isolated from beef pituitaries, or lysine if from hog pituitaries, in place of leucine.

Since all the preparations which have been used for the induction and stimulation of labor have been contaminated with small but nevertheless measurable amounts of another activity, one can rightly speculate as to whether or not the oxytocic activity is due to oxytocin alone or whether the vasopressin also is important. This sort of speculation has a basis since many use Pituitrin essentially interchangeably with Pitocin for induction, reserving the Pitocin for only those patients in whom a pressor substance might be contraindicated. Such users usually state that they cannot observe any differences in the effectiveness of the two preparations. Further, in a series of experiments on muscle strips from pregnant human uteri in 1943, C. Scott Russell³⁹ in England had concluded that the oxytocic activity of Pitocin can be completely accounted for by its content of vasopressin. Dahle⁴⁰ in Norway in 1950 reached essentially similar conclusions.

On the other hand Chassar Moir⁴¹ in England had earlier (1944) reviewed and studied this question and concluded that the response of the uterus to posterior pituitary hormones was a function of "the physiological state of the uterus at the time of the test." He showed that Pitocin did not have, and Pituitrin did have an oxytocic effect on the nonpregnant uterus. Though both hormones had an oxytocic effect on the pregnant uterus, Pitocin was much more active during labor and the first few days post partum. He pointed out further that "the response to pituitary extracts of an isolated muscle strip suspended in saline bath does not necessarily reflect the behavior of the intact uterus to these substances." Data accumulated by Ruskin⁴² working with du Vigneaud and in our clinic using the pure preparations of du Vigneaud tend to support these conclusions.

With the pure preparation of oxytocin, from both natural sources and synthetic, available to us in small quantities through the generosity of Dr. du Vigneaud, we have been able to test whether or not pure oxytocin will stimulate and induce labor in the human being.⁴³ So far we have carried on completely or in part 7 inductions and 4 stimulations of labor with the pure oxytocin from natural sources and 3 inductions and 3 stimulations with synthetic oxytocin. In so far as we can determine, the pure oxytocin, whether from natural sources or synthetic, is just as active, *unit for unit*, as is Pitocin. Thus it appears that oxytocin has oxytocic activity in the pregnant woman near term.

Following the synthesis of oxytocin by du Vigneaud and his associates Boissonnas and co-workers⁴⁴ in Switzerland in 1955 reported an alternative synthesis which results in oxytocic activity in the reaction mixture. Such synthetic oxytocic activity has been prepared by Sandoz Pharmaceutical and is now marketed in Europe under the trade name of Syntocinon. Several papers have appeared describing the pharmaceutical properties^{45, 46} and the

clinical use^{47, 48} of this preparation. It, too, seems clinically indistinguishable from "natural oxytocin" or from Pitocin for the stimulation and induction of labor in the human.

Thus from observations made with pure natural and synthetic oxytocin and with a synthetic reaction mixture containing oxytocic activity it can be concluded that oxytocin has an oxytocic effect in the human patient which is inherent in its molecular structure.

Now that the chemical structures of oxytocin and vasopressin are known it is not surprising to find there is some overlapping of activities. Rather, it is surprising that there is such a marked difference in their activities. Thus, though it is theoretically possible that vasopressin might have more oxytocic activity than oxytocin as suggested by Russell and Dahle, some preliminary study in our clinic in which lysine vasopressin isolated from hog pituitaries has been used for the induction and stimulation of labor does not seem to support this contention. On the contrary, vasopressin seemed to have much less oxytocic activity than oxytocin in the patient near term.

We might, at this point, briefly consider some aspects of dosage terminology in the use of this drug. The early preparations were described as being equivalent to a certain amount of the gland. They were marketed as ampules containing 1 ml. or 15 minims of solution. Thus the early users had little choice, except to describe their dose in terms of the volume of solution given. However, this practice, which grew out of necessity, has unfortunately continued to the present day even in spite of the fact that posterior pituitary preparations have been labeled in terms of units since 1925.⁴⁹ We should like to take this opportunity to urge that we learn to think of and report our dosages of oxytocin in terms of units rather than in terms of minims, which have actually no meaning.

Milk-Ejection Activity

The oxytocic, pressor, and antidiuretic activities of extracts of the posterior pituitary gland are well known and extensively used in medical practice. Less well known is the fact that injection of posterior pituitary extracts will initiate in the lactating animal an ejection or "let-down" of milk.

This effect was first observed by Ott and Scott⁵⁰ in 1910 in lactating goats. These observations were confirmed many times subsequently. Experimental work in animals has led to the conclusion that the release of posterior pituitary hormone is the normal efferent humoral stimulus for the flow of milk in response to the neural stimulus from the nipples to the hypophysis resulting from the suckling.

Experimental work in animals by Petersen,⁵¹ Turner and Cooper,⁵² Ely and Petersen,⁵³ and others resulted in a question as to whether or not this activity of the posterior pituitary was due to oxytocin, vasopressin, or a separate hormone. Isolation of the pure hormones by du Vigneaud and his group has enabled Whittlestone⁵⁴ and Cross and Van Dyke⁵⁵ to demonstrate in experimental animals that both oxytocin and vasopressin have milk-ejection activity inherent in their molecular structure. However, oxytocin is about five times as active as is vasopressin.

The use of this physiological activity of posterior pituitary hormones in the practice of medicine has been extremely limited. Newton and Newton have, relatively recently, from 1948 on, published a series of papers⁵⁶⁻⁶³ describing the use of Pitocin for eliciting milk ejection in parturient lactating females. They have suggested that Pitocin could be of use for reducing breast engorgement.

Our interest in this area was stimulated by Dr. du Vigneaud's telling us of the results obtained with oxytocin in the experimental animal. With the pure hormone available, it seemed logical to start our studies by first determining the dose required to elicit this milk-ejection response in the normal lactating woman.⁶⁴ Newton and Newton had used 3 units of Pitocin intramuscularly and subcutaneously. This dose produced an adequate response. But there are some indications from animal experiments that possibly a smaller dose might be effective. Therefore, we have determined, first, the dose of pure oxytocin required to produce consistently a milk-ejection response in the normal lactating woman.

The subjects for this study were all recently parturient women who were still in the hospital. They were selected because they had milk in their breasts. That is, they were at least four days post partum. The injections were made shortly before these mothers were to feed their babies. Appearance of milk at the nipple of one or both breasts was considered a positive response to the injection of oxytocin. Reports by the patients of sensations in the breasts or chest were not considered as positive responses.

With this as a test procedure, we have found that 2 units administered intramuscularly elicits a positive response consistently, within 60 seconds of the time of injection. One-half a unit, administered intravenously, elicits a positive response within 45 seconds of the time of injection. Some idea as to the order of magnitude of the potency of this hormone can be obtained when one considers that this dose is just 1 microgram or 1 thousandth of a milligram of hormone. Smaller doses may elicit a positive response, but they do not do so as consistently as the doses described.

The response obtained in these patients from the injection of oxytocin varies widely, from the showing of a bead of milk at one breast to the actual ejection of a stream of milk for a distance of 1 to 2 cm. from the nipples. The great majority, however, respond with a dripping of milk, either from both breasts or from the breast to be used for the approaching feeding. This flow of milk is transitory, lasting generally for less than 1 minute. When the baby is put to the breast shortly thereafter, the mother usually reports that the baby is able to obtain milk with what appears to be and feels to her like less effort than previously.

Both the intramuscular and the intravenous routes for the administration of the hormone are practical in the hospital. But they are not satisfactory to evaluate the usefulness of this hormone in helping a lactating mother with her first child adjust to her new home situation which arises immediately after she has left the hospital. With this time in mind, we are in the process of evaluating some simple means for administering the hormone either transbuccally or sublingually.

We have already made some preliminary trials with one technique which seems to hold some promise. Small circular disks of filter paper are impregnated with a solution of the hormone. Then they are air dried. The patient places one of these disks under her tongue a short time before she is to nurse. Milk ejection responses with this technique in normal patients have been sufficiently encouraging to warrant further study. However, the dose required is relatively large and the time for the response to occur is longer than with either the intramuscular or intravenous routes of administration.

These studies to date have been conducted with normal lactating mothers. They, however, need no injection of hormone to elicit the milk-ejection response. After all, it is a normal physiological response. But we all know of patients who say they desire, and apparently do, to breast feed their infants

and seem to have milk, but, for some reason or another, seem unable to nurse their infants adequately. We are now trying to determine if oxytocin will be of any value in such cases.

Oxytocin does not seem to be particularly effective until there is milk in the breasts. Thus, it is not to be expected that it will be of much use in the treatment of simple engorgement due to venous and lymphatic stasis which occurs on the second to fourth postpartum day. Support of this view is found in the 1953 report of Ingelman-Sundberg⁶⁵ of Sweden who showed that oxytocin is not of much value in treating early breast engorgement, though it was found of value in cases of late engorgement. Haeger and Jacobsohn⁶⁶ in Sweden in 1953 and Newton⁶⁷ again in 1956 recommended the use of oxytocin in mothers with breasts painfully engorged with milk. We too have had some limited experience with its use in a few cases in which the breasts have been engorged with milk and the infant has been unable to obtain sufficient milk to satisfy its needs. The results in such cases have not been particularly dramatic. But softening of the breast has been observed, with the infant obtaining sufficient milk at a feeding so that supplemental feeding became unnecessary. Unfortunately, with early ambulation and short hospital stays, with the patients going home on the fifth to sixth hospital day, we do not have much opportunity to evaluate this sort of complication.

Oxytocin combined with antibiotics has been found quite useful in treating mastitis in cows.⁶⁸ We hope to obtain more information on this question in the near future. At the present time, it can be said that we need much more clinical data along all these lines before we can adjudge the place of oxytocin in the treatment of complications of the breasts and lactation.

Intravenous Use for Induction of Labor

The intravenous method of administration of Pitocin was begun at the New York Lying-In Hospital in July, 1948. Since this time, through 1955 (Table I), this hormone has been given to 2,471 patients for the induction and stimulation of labor and to an additional 1,153 patients following cesarean section. What we have to say about the use of the hormone by this method is then largely an outgrowth of our own experience in testing this method of using the drug.

Generally accepted indications for the induction of labor are severe pre-eclampsia, severe renal disease, hypertensive disease, diabetes, and prolonged pregnancy. Partially accepted indications are mild pre-eclampsia, premature rupture of membranes, intrauterine death, missed abortion, and premature separation of the placenta. Less generally accepted indications are the so-called selective inductions because of the distance of the patient's home from the hospital, previous precipitate labor, or for the convenience of the obstetrician. We do not consider these last to be acceptable indications except in unusual circumstances.

TABLE I. INTRAVENOUS PITOCIN DRIP CASES, JULY, 1948, TO DECEMBER, 1955

Stimulations	1,509
Inductions	962
Total	2,471
Post cesarean section	1,153

Indications for stimulation of labor are desultory labor (primary or secondary inertia), lack of descent and/or rotation, intrapartum infection, twins, following the birth of the first twin, and premature separation of placenta.

Previous cesarean section for cephalopelvic disproportion is an absolute contraindication to the use of intravenous Pitocin. Relative contraindications are cephalopelvic disproportion, grand multiparity, abnormal presentation, previous cesarean section, and fetal distress.

Inductions, generally being elective, should be started in the morning after the patient has had a good night's sleep. A thorough evaluation of her pelvis should have been made. A vaginal examination is always done prior to induction to determine accurately the condition of the cervix, the station of the presenting part, etc. The induction is carried out on the labor and delivery floor under constant observation. If the induction is unsuccessful after six to eight hours, it is discontinued.

In the occasional patient in whom induction is indicated weeks from term, in whom the cervix is unfavorable and the presenting part high, several courses will usually be required to achieve delivery. In general, the two or three courses necessitated are administered on succeeding days. We have not administered more than three courses because of the physical and psychic trauma involved.

We use a two-bottle method. One bottle contains Pitocin, the other bottle is free of the hormone. The tubing from both bottles joins just before entering the needle. With this arrangement the infusion is started with a solution free of Pitocin. Then the Pitocin solution is gradually introduced until the desired response is obtained, i.e., contractions of the uterus comparable to those observed in normal spontaneous labor.

With this two-bottle setup a few drops of the Pitocin solution may be infused to test the sensitivity of the patient to the hormone. Contractions may be instituted gradually and the concentration of the hormone in the infusion fluid can be readily changed. The infusion of Pitocin may be discontinued almost immediately, and the Pitocin-free solution continued if violent labor ensues, during forceps operations, or for other reasons. The Pitocin solution may be restarted post partum and continued through the third and fourth stages of labor.

For inductions 3 units (4.5 minims) of Pitocin are usually added to 500 ml. of the infusion fluid; for the stimulation usually 2 units. The infusion is started with the Pitocin-free solution. Then several drops of Pitocin-containing solution are added and any untoward reactions in the patient are simultaneously watched for. If any are observed the Pitocin is discontinued. The infusion of the Pitocin-containing solution is gradually increased until in about 30 minutes only the diluted Pitocin infusion is running. Scrupulous attention to these details is needed to avoid initial prolonged contractions or shock in patients sensitive to the drug.

If the response of the patient is not satisfactory with the initial concentration and the Pitocin has to flow at a rate greater than 40 drops per minute the amount of Pitocin in the hormone-containing bottle is increased until the desired result is obtained. As one might expect, some few patients, with labor once started, seem to continue on their own. Others, however, require that the concentration of the hormone in the infusion fluid be constantly increased to achieve the desired result, i.e., contractions which simulate those observed to occur progressively during a good normal spontaneous labor. Though the primary objective is to get the patient delivered, every attempt is made to obtain contractions which simulate those obtained in normal spontaneous labor. Forcing labor is definitely contraindicated. The concentration and amount of hormone used are a function of each individual patient.

The total amount of hormone usually required for a stimulation is between 1 and 4 units and for an induction, 2 and 8 units. Great variation in

amount required has been observed, however. The extent of this variation can be better appreciated by the fact that the total amount of hormone used to accomplish an induction or stimulation has ranged from 0.008 to 233 units (0.012 to 350 minims). The largest total amount given was quite unusual, 100 units being the next lowest amount used. These large amounts of hormone are given under rather unusual circumstances and are not necessarily recommended. This has indicated, however, that with careful supervision and the use of the two-bottle technique it is possible to increase the concentration of Pitocin in the infusion fluid to quite high concentrations and still have essentially normal types of response. After all, it is a normal response we are attempting to achieve and the concentration or amount of the hormone used becomes important only in this respect.

Following the institution of the Pitocin drip certain observations are carried out at frequent intervals. These include the fetal heart rate, the uterine contractions, and the maternal blood pressure and pulse which are plotted graphically and included in the chart. Of the four observations the fetal heart and the uterine contractions are most important and absolutely necessary. The maternal blood pressure and pulse show only slight occasional variation and need not be followed as closely. It is our practice to have the patient under continual observation by a doctor. If in an emergency she is to be left unattended the oxytocin infusion is stopped and the glucose solution continued to maintain the system.

Data (Table II) on all the inductions of labor during 1954 and 1955 show that approximately half were accomplished by simple artificial rupture of the membranes or this combined with medical means. Thus it seems inadvisable to rupture membranes and start intravenous Pitocin simultaneously for the Pitocin may be unnecessary. Further, by combining the two one may cause an undesirable tumultuous labor.

TABLE II. INDUCTIONS AND STIMULATIONS OF LABOR

	1954	1955	TOTAL
<i>Without Pitocin.—</i>			
Artificial rupture of membranes only	151	192	343
Medical induction only	20	12	32
Artificial rupture of membranes with medical induction	12	2	14
Total	183	206	389
<i>With Pitocin.—</i>			
Pitocin only	101	107	208
Pitocin with artificial rupture of membranes	46	47	93
Artificial rupture of membranes with Pitocin stimulation	60	73	133
Total	207	227	434
Per cent of deliveries	5.1	5.5	5.3
Stimulations only	308	303	611
Per cent of deliveries	7.7	7.4	7.5

TABLE III. PITOCIN INDUCTIONS AND STIMULATIONS AND CESAREAN SECTIONS AMONG DELIVERIES, 1952-1955

	1952	1953	1954	1955	TOTAL	PER CENT
Deliveries	4,149	3,963	4,022	4,097	16,231	
Pitocin inductions	146	133	147	154	580	3.6
Pitocin stimulations	205	188	368	376	1,137	7.0
Cesarean sections	211	174	168	183	736	4.5

An additional breakdown of the figures (Table III) shows no actual increase in recent years (1952-1955) in the use of the intravenous Pitocin drip

for induction or at the time of cesarean section, whereas there has been a definite increase in its use for stimulation of desultory labor. This we believe is the way it should be. Even with increased safety in its use, we believe strongly in reserving this method for definitely indicated cases and condemn the present trend toward the "wholesale" induction of labor.

Conclusions

1. Chemically pure oxytocin from both natural and synthetic sources is capable of initiating and stimulating labor at or near term. It is also capable of initiating milk ejection.

2. The use of oxytocic hormone for milk ejection and in breast complications requires further evaluation and its clinical usefulness is yet to be determined.

3. The intravenous use of the oxytocic hormone (Pitocin) for the induction and stimulation of labor is generally well established. Used under the conditions described it is safe for the mother and baby. If the conditions cannot be fulfilled the hazards are too great to justify its use.

4. Susceptibility of the uterus to oxytocin in patients at or near term seems to vary tremendously, some individuals requiring many times as much as others for the induction or stimulation of labor.

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STUDIES ON THE SUPPRESSION OF LACTATION BY HORMONES*

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THE socioeconomic structure of our civilization causes an increasing number of mothers to prefer not to nurse their babies. Consequently, the inhibition of lactation in the puerperium presents a waxing problem.

Earlier work with laboratory animals indicated that estrogens exhibited an inhibitory effect on lactation.^{1, 2} This led to numerous clinical studies on the use of estrogens to inhibit lactation in the puerperium.³ Over the years a large number of synthetic and natural estrogens have become available for clinical use and many have been used with varying degrees of success in suppressing lactation. One of the newer synthetic estrogens is TACE† (chlorotrianisene).

The purpose of this study was twofold: (1) to determine the effectiveness of two different compounds in suppressing lactation and preventing painful postpartum breast engorgement, and (2) to compare this with the effectiveness of stilbestrol and a placebo. The two preparations under scrutiny were TACE and Premarin with methyltestosterone.‡

TACE is the proprietary name for tri-*p*-anisylchloroethylene. It is a synthetic preparation falling in the class of pro-estrogens which are derivatives of triphenylethylene.⁴ Its structural formula resembles that of diethylstilbestrol and hexestrol in having two phenyl groups separated by two carbon atoms. Like the former and unlike the latter, these two carbons are unsaturated. It differs from these two also in that the two hydroxyphenyl groups are replaced by two methoxyphenyl groups and the two ethyl groups at the separating carbons are replaced by a third methoxyphenyl group and a chloride group.⁵ It is relatively inactive in its unchanged form but on absorption from the gastrointestinal tract, it is converted to an unknown intermediate compound. This conversion is believed to take place in the liver.⁴ TACE also has the peculiar property of being stored in body fat, whence it is released slowly, thus producing a sustained effect for a longer period of time and preventing the abrupt withdrawal of the pharmacological effect when administration is stopped.^{6, 7, 8} It also appears that a saturation point is reached in the concentration in body fat.⁷ Enlargement of the pituitary is also said not to occur.⁸

*Presented at the Twelfth Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Murray Bay, Quebec, June 8, 9, and 10, 1956.

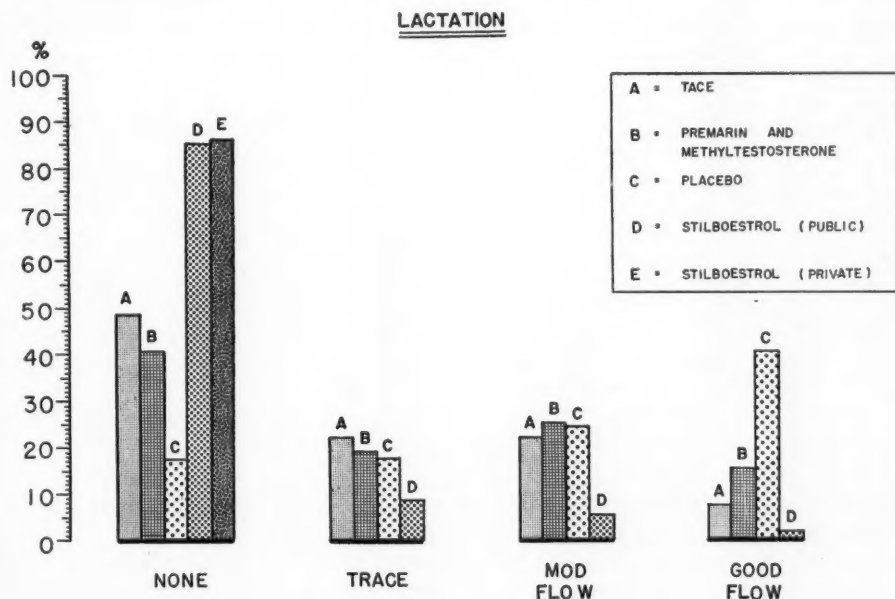
†The TACE used in this investigation was supplied by the Wm. S. Merrell Company, Cincinnati, Ohio.

‡The Premarin with methyltestosterone and the stilbestrol in enteric-coated tablets were supplied by Ayerst, McKenna and Harrison Limited, Montreal, Canada.

In the past few years an increasing number of reports have appeared on the clinical use of TACE in conditions commonly treated with estrogens, i.e., the menopause⁹⁻¹² acne,^{13, 14} carcinoma of the prostate,¹⁷⁻¹⁹ carcinoma of the breast,^{15, 16} and suppression of lactation in nonnursing mothers.^{5, 20, 21}

Material and Methods

The patients in this study, except for a small additional group mentioned later, were from the public obstetrical service of the Royal Victoria Montreal Maternity Hospital. Their decision not to nurse was known to us prior to delivery. They numbered 215 and the only common factor was their decision not to nurse. Such factors as age, parity, and previous nursing were disregarded.



The nonnursing mothers in our hospital are segregated from nursing mothers and cared for on a different ward and by a separate staff of nurses. The ward is divided into four sections of four beds each. Because of this physical layout it was simple to divide the ward into sections A, B, C, and D and assign to the patients in each section one of the four preparations. There was no selection of cases for the various groups, new patients simply being placed in whatever bed happened to be empty. The number of patients and dosage used in each group are recorded in Table I.

TABLE I. DISTRIBUTION AND DOSAGE OF DRUGS

DRUG	NO. OF CASES	DOSAGE
A. TACE	68	One 12 mg. capsule four times a day for eight days
B. Premarin with methyl testosterone	54	Three tablets, each containing 1.25 mg. Premarin and 10 mg. methyltestosterone, every four hours for five doses, starting immediately after delivery
C. Placebo	45	One capsule four times a day
D. Stilbestrol	48	5 mg. three times a day for three days, followed by 5 mg. twice a day for three days, followed by 5 mg. a day until home

Medication was given by the nurses, who did not know the composition of the capsules and tablets. Otherwise the routine of the ward was not changed. Fluids were not restricted, breasts were supported by a Murphy-type binder and the only analgesic used was aspirin with codeine, $\frac{1}{8}$ grain. The latter was given when requested by the patient and this was recorded in the chart. All patients were kept in the hospital for seven to nine days as is our custom. Those who refused to remain this long were eliminated from the survey.

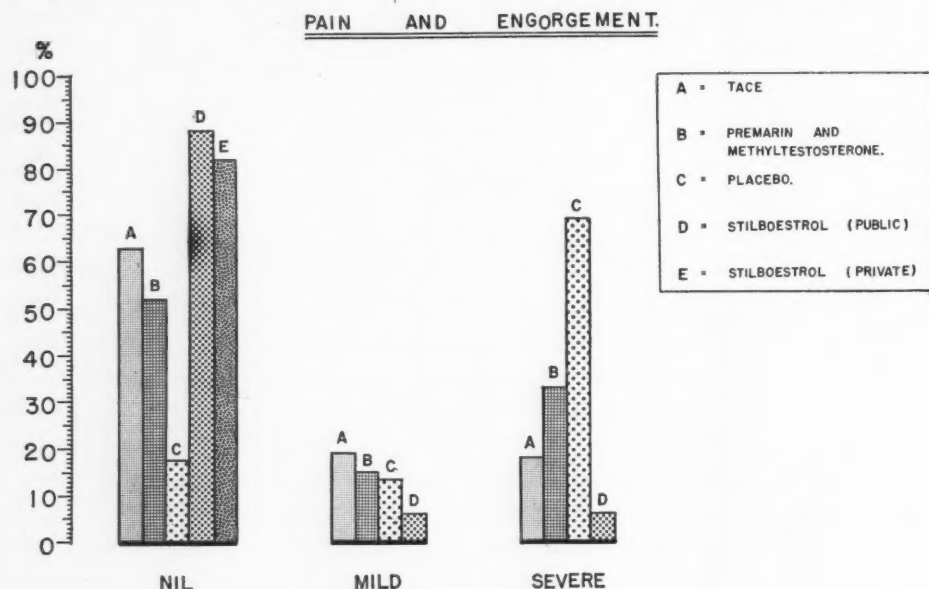


Fig. 2.

Investigation of the family history, past history, antenatal course, type of labor and delivery, blood loss, and anesthetic was rather exhaustive but since none of these factors showed any correlation with the results we have eliminated them from the report. After delivery a daily inspection of the breasts was carried out with special attention to engorgement, color, pain, tenderness, temperature, and amount of milk. The frequency of requests for analgesics was noted. Lactation was noted as being absent, or present \pm , +, or ++. The plus-or-minus category signifies only a drop of milk on gentle pressure from either breast on one occasion only, one plus when milk was easily expressed and leaking, and two plus, a frank flow of milk. Pain, engorgement, etc., were also graded on a \pm , +, and ++ basis, and the presence or absence of nausea and vomiting noted.

The follow-up consisted of an interrogation by one of us at the routine visit six weeks post partum. This was aimed at determining whether there had been a reappearance of milk, engorgement, pain, or tenderness. Inquiry was also made as to persistence of lochia, occurrence of vaginal bleeding, and whether or not menstruation had reappeared. No special note was made as to the degree of involution of the pelvic organs.

Results

The best results were obtained with stilbestrol both during the immediate puerperium (Tables II, IV, and V, and Figs. 1 and 2) and for the entire six-week period following delivery (Table III and Fig. 3). This was somewhat

surprising since in a previous investigation of stilbestrol as an inhibitor of lactation, during which 260 private patients were observed, results were no better than those obtained with TACE in this series. On close scrutiny of various factors, the only difference appeared to be in the timing of the first dose in relation to the delivery. In the series of private patients the first dose had sometimes been delayed for 36 to 48 hours. Consequently, a second group of private patients was observed from August, 1955, to January, 1956. The same dosage schedule as shown in Table I was followed. The first dose, in every case, was given no later than eight hours after delivery. As may be seen in Table IV and Figs. 1 and 2, the results were practically identical with those obtained in the public group. Because of this, further breakdown into \pm , +, and ++ was not carried out, nor were these patients subjected to the interrogation at six weeks.

TABLE II. GRADING OF SIGNS AND SYMPTOMS DURING IMMEDIATE PUERPERAL PERIOD

	A. TACE, 68 CASES				B. PREMARIN AND METHYLTESTOSTER- ONE, 54 CASES				C. PLACEBO, 45 CASES				D. STILBESTROL, 48 CASES			
	0	\pm	+	++	0	\pm	+	++	0	\pm	+	++	0	\pm	+	++
Color of breasts																
Normal																
Red																
Lactation	33	15	15	5	21	10	14	9	8	8	11	18	40	4	3	1
Pain	43	13	11	1	27	8	11	8	8	6	18	13	42	3	3	0
Engorgement	52	3	12	1	30	4	13	6	12	2	11	20	46	2	0	0
Other treatment	60	1	7	0	49	2	2	1	28	1	2	14	48	0	0	0
Nausea	67	0	0	0	53	0	1	0	44	0	1	0	48	0	0	0
Vomiting	67	0	0	0	54	0	0	0	43	0	2	0	48	0	0	0

TABLE III. GRADING OF SYMPTOMS DURING SIX-WEEK PUERPERAL PERIOD

	A. TACE, 49 CASES				B. PREMARIN AND METHYLTESTOSTER- ONE, 54 CASES				C. PLACEBO, 45 CASES				D. STILBESTROL, 48 CASES			
	0	\pm	+	++	0	\pm	+	++	0	\pm	+	++	0	\pm	+	++
Milk reappeared or present	39	2	3	5	49	2	3	0	27	2	14	2	43	2	3	0
Pain recurred or present	45	1	2	1	50	2	2	0	23	1	14	7	46	1	1	0
Bleeding	48	1	0	0	52	0	2	0	31	8	5	1	46	2	0	0
Period	29	0	20	0	35	0	18	0	25	0	20	0	38	0	10	0

TABLE IV. RESULTS IN 49 PRIVATE PATIENTS ON STILBESTROL STARTED IMMEDIATELY AFTER DELIVERY

Complete suppression of lactation	42
Absence of pain and engorgement	40

TABLE V. COMPOSITE FIGURES FOR COMPLETE ABSENCE OF LACTATION PAIN AND ENGORGEMENT EXPRESSED IN PERCENTAGES

TACE	62.8
Premarin with methyltestosterone	48.1
Stilbestrol	88.8
Placebo	20.7

Unfortunately, because of a lapse in record keeping beyond our control, only 49 of the 68 patients treated with TACE were seen at follow-up. Results with TACE were good but only slightly better than those with Premarin with

methyltestosterone. By far the poorest results obtained in our series were those shown by the placebo group, both in the immediate puerperium and throughout the six-week postpartum period, and the only cases of bleeding severe enough to cause concern were all from this group. There were 3 of these; 2 of the patients had to be readmitted to the hospital.

As for nausea and vomiting, there was no case attributable to any of the medications used.

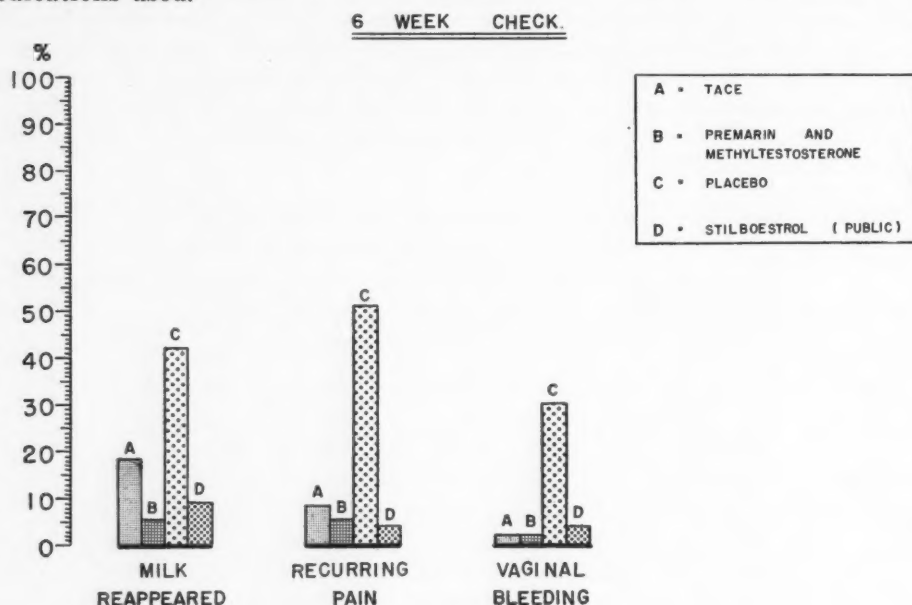


Fig. 3.

Comment

Although our results with stilbestrol are not quite as good as those reported by others,²⁵ it is difficult for us to agree with Kosar and associates²³ who, using dienestrol, concluded that estrogens are of no use in suppressing lactation since their results showed suppression in only 13 per cent of treated cases while their untreated group showed 65 per cent complete inhibition. Romani,²⁴ using dienestrol also, found it effective and graded its effectiveness as seven and a half times that of diethylstilbestrol. TACE did not give as good results in suppressing lactation and preventing pain and engorgement as has been reported by others,^{5, 20, 21} but the low incidence of bleeding is in line with that previously reported.

Premarin with methyltestosterone gave results slightly better than those in the control group but, if the figures for suppression of lactation and prevention of pain and engorgement are combined, the difference is greater (Table V). Still, they do not reach those of other authors using a combination of estrogens and testosterone. Comparison must be guarded, however, since the compound used by Katzman²² was a parenteral preparation of estradiol benzoate with testosterone propionate. Our results are significant, we believe, when it is remembered that treatment with this preparation was for twenty-four hours only.

Summary

Two hormone preparations, TACE and Premarin with methyltestosterone were compared to stilbestrol and a placebo in their effectiveness in suppressing lactation and preventing pain and engorgement of the breasts in 215 non-nursing mothers. The synthetic estrogen, TACE, has been found to give good results which are fairly closely approximated by Premarin with methyltestosterone. The best results in this survey, however, were obtained with stilbestrol, while the control group receiving a placebo showed the poorest results.

Conclusions

1. TACE, given in doses of 12 mg. four times a day for eight days will provide good results in elective suppression of lactation with very few side effects save a slight lengthening of the brown lochia stage of involution.

2. An intense course of Premarin with methyltestosterone given over the first twenty-four hours following delivery will give results closely approximating those of TACE.

3. Stilbestrol given by our dosage schedule, as enteric-coated tablets, gives results somewhat better than either of the other preparations.

4. When elective suppression of lactation is contemplated, medication, no matter what it is, should be started as early as possible in the puerperium, preferably during the first eight hours.

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Discussion

DR. GEORGE M. WHITE, St. John, New Brunswick.—One is more or less forced to accept the results obtained because of the thoroughness of the investigation.

My greatest concern in the postpartum care of the breasts that are not being used for nursing is infection. Lactation can be recorded only when the breasts are tested for milk, and I think squeezing the breast to determine the presence or absence of lactation is a breast stimulant.

In our clinic, our own staff and most of the general practitioners have given up medication for the suppression of lactation. If our patients express during the prenatal period the willingness and the desire to nurse, they are given instructions on preparing their breasts for nursing. If they are not keen on nursing, this instruction is not given. After delivery, we simply support the breasts well. Fluids are not restricted. The patients are given an ordinary diet. If the breasts become slightly firm, we sometimes use an ice bag and an aspirin compound, and in twenty-four to thirty-six hours the tension in the breast has reached maximum. We have very few, if any, complaints. Certainly we have less trouble in the way of complaints or even with infected breasts than we used to have.

We have gone through the era of hormones, and I will admit, after reading Dr. Primrose's paper, that we probably used our hormones too little and too late, but we are firmly convinced in our clinic that, when the breasts are well supported, left strictly alone, and not in any way stimulated to test for lactation, or even to test for engorgement, after twenty-four to thirty-six hours the pressure in the breast is greater than the secretive power, and we are better off in this way. I can state that during the year 1955 we had 1,450 deliveries and only 2 abscesses.

NOVOCAIN AS AN ABDOMINAL RELAXANT*

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DURING the years of World War II when anesthetists were scarce and anesthesia often very unsatisfactory, I became interested in the use of local anesthesia in abdominal surgery. Over many hundreds of cases I worked out techniques that enabled many major procedures to be done satisfactorily and found local anesthesia completely safe and free of toxic effects. It did require either a fairly heavy amount of sedation or the use of gas, oxygen, and Pentothal to keep the patient sleepy or lightly asleep, to get the most dependable results. It did take a little extra time and required gentle handling of tissues, a point not a complete disadvantage from the patient's viewpoint.

With improved general anesthesia and a more plentiful supply of anesthetists there will not likely be very wide interest in the use of local anesthesia for its own sake; so I do not propose to stress this aspect of the subject and will mention only briefly a few points about it as an introduction. My intention is to stress two real benefits which this study has shown can be applied to certain cases in abdominal surgery, regardless of the anesthetic being used.

First, briefly, a record as to the technique evolved for its use as an anesthetic. This involved three phases:

1. Local infiltration of the skin and muscles of the abdomen in the line of the incision, with fanning out on either side to give good muscle relaxation.
2. Anesthetizing of peritoneum and all peritoneum-covered organs by the simple procedure of pouring about 200 c.c. of $\frac{1}{2}$ per cent Novocain into the abdominal cavity. This is perhaps best done through a small incision in the peritoneum before the patient is put in Trendelenburg position, the peritoneal opening then being clamped with forceps to prevent loss of solution while the bleeders in the abdominal wall are tied. The Novocain thus free in the peritoneal cavity rapidly diffuses throughout the abdomen and anesthetizes it; by the time the bleeders are tied the patient can be lowered, the abdomen freely opened, and the operation continued.

3. Special techniques for individual organs may be necessary:

A. In appendicectomy, a few drops of Novocain should be injected into the mesoappendix.

In ovariectomy and in hysterectomy, similarly, some Novocain should be injected between the layers of the broad ligament; not much is needed. For total hysterectomy an additional preliminary procedure is needed; when the vagina is being painted with Gentian violet before the operation is begun, some Novocain is injected into the paracervical tissues through the vault of the vagina.

*Presented at the Twelfth Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Murray Bay, Quebec, June 8, 9, and 10, 1956.

For classical cesarean section, no supplementary injection is needed as the body of the uterus is insensitive; but for low segment cesarean section it is necessary to infiltrate under the fold of the bladder peritoneum.

B. Bowel resection or anastomosis does not require any more than the basic procedure of free Novocain in the abdominal cavity.

Now I do not intend to elaborate on these techniques nor to stress the use of local anesthesia in doing gynecological surgery, as I have no expectation that anyone at the present time is going to adopt this as a routine procedure. A few years ago, with poorer anesthesia, I think there could have been a fairly wide field for this, especially in poor risk cases. I no longer use it routinely as our anesthesia is now good and I do not need to carry out this slightly slower technique.

Nevertheless I would like to say that over a period of several years I found it an eminently safe and satisfactory type of anesthetic and never regretted using it; and not once in many hundreds of cases did I ever find the slightest suggestion of Novocain poisoning or reaction, either early or late.

Besides its safety, the other very noticeable feature observed in using this method was the excellent relaxation provided. The local infiltration of the abdominal muscles as part of the technique of local anesthesia relaxed them as much as a spinal anesthetic. If necessary, about three extra injection points far out on the lateral walls into the oblique muscles could be used to obtain still better relaxation; although usually injection of the rectus muscles alone was enough. I do not like to use self-retaining retractors, and this was certainly unnecessary with the good relaxation of muscles thus obtained.

Even more striking was the way the intestine disappeared from sight. The intra-abdominal Novocain caused the gut to shrink up to lead-pencil-like dimensions; no abdominal packs were needed as the intestine simply was not present in the field of operation. This phenomenon is even more marked with intra-abdominal Novocain than with spinal anesthesia. This simplifies the operative procedure, avoids the disturbing effect of a pack, prevents traumatizing the gut, eliminates any struggle to close the abdomen, and makes for smooth convalescence.

The interesting thing about these observations is that they are true when Novocain is used in this way to supplement other anesthetic agents. Regardless of whether ether, gas, Pentothal, or a spinal anesthetic is being used, local infiltration of Novocain into the abdominal wall will give extra relaxation; this infiltration need not be done at the beginning of an operation, but can be done at any stage when extra relaxation is found advisable.

It is true that with the advent of curare into the armamentarium of the anesthetist there is less occasion to make use of Novocain; a few years ago it was often the only method of obtaining needed extra muscle relaxation; now it is only an alternative, although a quick, easy, safe, and efficient method.

As to the other benefit—shrinking up distended intestine—Novocain is still the most efficient agent. Regardless of the type of anesthetic used, still more shrinkage of gut may be obtained by pouring about 200 c.c. of 1/2 per cent Novocain into the open abdomen. If done at the beginning of the operation, this will prevent the intestine from becoming troublesome. This method may be resorted to at any stage, however, with very prompt response. If it is not too difficult, the Novocain may be simply poured into the open abdomen; if loops of gut are coming out and the abdomen is overfilled with such uncontrolled, distended loops, it may be impossible to pour it in. In this case, it may be sprayed on the surface of the presenting loops with a syringe; then further syringefuls of Novocain (no needle being used) may be injected beside and behind these loops into the space where lies the mesentery. Very quickly

the intestine will begin to retract and as the diminished coils shrink and subside into the cavity, more Novocain may be poured in. The exact amount is not critical; about 200 c.c. is an average amount, but more or less may be required. There is no ill effect from a larger quantity.

We have all seen cases (especially in the old days with ether) with tight abdominal muscles and straining guts, where the surgeon had to fight every inch of the way to operate or to close the abdomen. Such cases respond very quickly to treatment with Novocain.

Summary

An attempt has been made to show how Novocain may be used as an anesthetic in the field of gynecological abdominal surgery. Attention is drawn to its usefulness in providing both muscular relaxation and shrinking of bowel to small size. It is pointed out that these advantages may be obtained by the use of Novocain as an adjunct to any other type of anesthetic used in abdominal surgery. It is here, we feel, that its greatest use lies, as it can be called upon at short notice at any stage during an operation to provide whatever extra relaxation is required, or to shrink up troublesome loops of intestine.

Discussion

DR. C. V. WARD, Montreal, Quebec.—Dr. Grafton is to be congratulated on reminding us that local anesthesia can be used for the great majority of gynecological procedures when trained anesthetists are not available. This happened during the last war and may happen again in the event of a similar emergency.

It appears wise, therefore, for gynecologists to use local anesthesia often enough to ensure that they will have a working knowledge in case of necessity.

Are there any dangers in the use of Novocain as a local anesthetic or as an abdominal relaxant?

1. There is always the possibility of the patient's being sensitive to the drug.
2. There is often a pronounced lowering of the blood pressure, sometimes to the point of producing shock.

The second danger can be minimized by using general anesthesia in conjunction with the local. It has been noted that the greater the amount of general anesthetic administered, the less is the incidence of lowered blood pressure. It has also been shown that where a general anesthetic is not administered the patient should be given Nembutal pre-operatively, which also cuts down the incidence of lowered blood pressure.

Patients who are operated upon under a local anesthetic alone are often upset and feel pain, and are generally uncomfortable during the surgical procedure. I feel that this is unnecessary in hospitals where trained anesthetists are available, who are capable of administering a safe general anesthetic.

In the Montreal General Hospital one of our general surgeons uses Novocain as an abdominal relaxant. He uses a combination of general and local anesthesia. He opens the abdomen under general anesthesia and injects 1 per cent Novocain into the undersurface of the peritoneum and rectus muscles, producing satisfactory relaxation. He also injects the Novocain into the lesser sac when added relaxation is required. The relaxation is produced by action in the upper abdomen on the intercostal nerves, in the mid-abdomen on the dorsal nerves, and in the lower abdomen on the lumbar nerves.

When a dose of 200 c.c. of 0.5 per cent Novocain is poured into the abdomen, it produces its results by action on the local nerves to the gut, some of which are sympathetic.

At this point one should consider the effects of Novocain and also the more recently discovered relaxants which are injected intravenously.

It appears that a middle course should be adopted as follows: (a) induction of anesthesia by a general anesthetic; (b) the injection of a safe dose of Novocain into the peritoneum and rectus muscles to produce some relaxation; (c) the intravenous injection of another relaxant in a smaller dose than is used if no Novocain is administered.

This procedure would eliminate the necessity of artificial respiration for long periods of time, when the patient is unable to breathe spontaneously. I cannot help feeling that this deep relaxation may cause some serious aftereffects to the patient concerned.

The maximum dose of Novocain should not exceed 1 Gm., since larger doses have been proved to be extremely dangerous to the patient.

SOME BIOLOGICAL ASPECTS OF SPONTANEOUS ABORTION*

Review of the Recent Literature

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SPONTANEOUS abortion at some stage in its progress from threat to completion is one of the commonest conditions for which gynecological advice is sought, and, though diagnosis is usually easy, prognosis is often difficult and treatment frequently disappointing.

All will agree that spontaneous abortion is largely a complication of the first trimester of pregnancy. The great majority of clinically recognizable abortions occur in the second and third months. The average date for the first symptom was the eighty-first day¹ in one series of 500 women who gave definite dates for their last menstruation and for their first sign of trouble. From that date till the period of viability the abortion rate became progressively lower.

The most casual study of the abortuses seen throughout the first twenty-eight weeks of pregnancy shows that the early ones are more often than not abnormal in the placenta and membranes, or in the embryo, or in both. As pregnancy proceeds, the proportion of morphological abnormality decreases and so does the abortion rate, while more and more often the placenta and fetus are grossly normal and clinically these abortions appear to be more like premature births, too premature to survive though not infrequently the fetuses may be born alive. The proportion of abnormality has been variously stated by different authorities. Keibel and Mall² say that 70 per cent of abortuses of the first month are abnormal, and 50 per cent of those of the first two months. Kaiser³⁻⁷ placed the rate of abnormality in 606 abortions of all stages at over 50 per cent and Hertig and Livingstone⁸ found 61.7 per cent abnormal in some respect out of 1,000 consecutive abortuses which they examined. Huntington,^{9, 10} who sent 103 abortuses from his private practice to Streeter to be examined at the Carnegie Institute, reported that he found 81.8 per cent to be abnormal "on the basis of failure to develop rather than on any characteristic histological difference in tissues." Since these reports covered abortuses of all stages, and in Hertig and Livingstone's series⁸ some fetuses were expelled alive, it is obvious that the proportion of abnormal early abortuses must have been very high.

Since abortion is so much more frequent in early pregnancy than in the second trimester, and abnormal ova are much more often found in early than in late abortion, it seems plain that abnormality of the fertilized ovum must be causally connected with abortion and that if we knew the reason for the abnormalities that are so frequent we should have found the cause for most early abortions. Thus we should have a clearer idea of prognosis and of the possibility of useful treatment in individual cases.

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For many years there have been two schools of thought about the etiology of pathological ova and of abortion, which both schools tacitly treat as being synonymous. The one holds that a normal ovum and a normal spermatozoon unite and form a normal zygote which is rendered abnormal, killed, and expelled by an abnormal maternal environment. The other, without denying that environment may play a part, holds that defective germ cells are at fault in a great majority of cases.

By those who first propounded the view that a good egg is damaged by a bad environment, the word was used in the narrow sense of the environment provided in the maternal uterus, and included fibroids, retroversion, and trauma, which today are not usually seriously considered as causing abortion. But the principal foundation for this theory is the work of Mall^{11, 12} and his associates. Mall asked for abortuses from all over the United States to be sent to him for study. Among those he received and studied, he noted two things in particular: the great frequency of abnormality of embryos or membranes or both, and the almost invariable presence of endometritis. He concluded that no matter how good the fertilized ovum might be, it could not develop normally in an infected endometrium; and that the endometritis caused a poor implantation and poor nutrition of a normal ovum, its anomalous development and abortion. That was in 1908, and he and Keibel² and Meyer¹² defended that position in their later works.

It was only in 1908 that Hitschmann and Adler¹³ first worked out the endometrial changes of the human menstrual cycle and showed that what had been called glandular endometritis was the normal gravid endometrium. Later Hertig and Livingstone⁸ pointed out that Mall^{2, 11, 12} had mistaken the sterile invasion of decidua about thrombosed vessels for infection. Furthermore, Huntington^{9, 10} showed with Streeter¹⁰ that in most abortions the embryo has long been dead before abortion occurs, and it is plain, as Kaiser⁶ stated, that when bleeding has gone on for days, there is inevitably an ascending uterine infection. Moreover, widespread experience with endometrial biopsies in all stages of the cycle has shown that endometritis at the time of implantation, which Rock and Hertig¹⁴ have shown to be about the twenty-first day (nineteenth to twenty-second day) of the normal cycle, is extremely rare. It appears therefore that endometritis is not the cause of abnormal development and abortion, but is their direct result.

Environment has a wider significance than Mall originally supposed. Maternal intoxications with some of the heavy metals and severe maternal infections have long been known to be occasionally the cause of fetal death and abortion. Litzenberg¹⁵ in 1937 stated that deficient thyroid function was a common factor in its etiology, and in 1948 and 1951, Delfs and Jones^{16, 17} stated that, though excretion of chorionic gonadotrophin, estrogen, and pregnanediol were frequently below normal values, low thyroid function was the most frequent finding in pregnancies which ended in abortion.

Warkany¹⁸ in 1948 reported that absence or very low levels of certain vitamins in the diet of experimental animals led to the development of definite and fairly specific congenital anomalies in their young. Ebbs, Tisdall, and Scott¹⁹ in 1941, Burke and her co-workers,^{20, 21} and Dieckmann and associates²² have presented statistical evidence that women whose diets are deficient have more abortions and congenital anomalies than do those whose diets are normal. Gregg²³ in 1941 showed the relationship of early rubella infection of the pregnant woman to certain definite congenital anomalies. Thiersch²⁴ has shown that a folic acid inhibitor which is known to cause the death and absorption of fertilized ova of rats and mice will cause abortion of human ova if given early enough in pregnancy.

Maternal intoxication and severe infections account for only a fraction of the abortions that occur, however, and, though thyroid function may affect the general bodily environment for good or ill, the basal metabolic rate is notoriously unreliable. Such deficiency states as Warkany produced in experimental animals can scarcely be found in pregnant women on the worst of diets and there is no general agreement on the effect of human diets on intrauterine development. The abortion rate among private patients whose diet can be to some extent controlled does not seem to differ greatly from that in the general population. Rubella, while it causes congenital anomalies, does not often cause abortion. And lack of folic acid in human diets has not been shown to play a part in spontaneous human abortion.

Mall was much influenced by the work of experimental teratologists which was done concurrently with his study of abortuses. They showed that all the congenital anomalies known to occur in man could be induced in the fertilized ova of sea urchins and other marine species by changes in concentration of salts in sea water or by mechanical damage. Continuing studies of this nature, however, have shown that identical anomalies can also be produced in the fertilized ova of birds and mammals as well as marine species by many different factors; and that nutritional deficiency, mechanical injury, exposure to radiation, certain chemical substances, and some maternal infections may produce identical anomalies in mammalian embryos. The one thing that all these diverse factors have in common is that the tissues and organs affected are acted upon at a critical phase of their development, and it does not seem to matter what the noxious factor is, the end results may be comparable or even identical. What is more important is that identical anomalies may be produced genetically.²⁵

In recent years it has been possible to study the output of reproductive hormones during the menstrual cycle, in normal pregnancies, and in pregnancies that end in abortion. It has been established^{5, 17, 18, 26} that in the latter the output of chorionic gonadotrophin is variable but usually lower than normal and that the pregnanediol output with rare exceptions is low in all such pregnancies and, no matter what its early level, it always falls before abortion. Studies of pregnanediol in the clinically normal cycles of patients who have previously aborted repeatedly are likely to show a low level of excretion and concurrent examination of endometrial biopsies shows a defective pro gravid phase which varies in intensity more or less directly with the pregnanediol level.^{26, 27}

Hughes and associates²⁸⁻³⁰ have seen in this evidence for Mall's view that a normal fertilized ovum embeds poorly and is poorly nourished, not indeed in an inflammatory endometrium, but in one that is defective because it is supported by a defective corpus luteum. This might be taken at first glance to be definite and final evidence that a bad environment harms and even destroys a good egg.

But what is it that provides the uterine environment in which the ovum, whether good or bad, must develop normally or abnormally? The corpus luteum by its secretion of estrogen and progesterone controls the development of the endometrium. If the amount and proportion of these hormones is normal, the endometrium will be normal. If they are not, it will be poorly developed. When the ovum is fertilized, as it embeds itself about the twenty-first day, the trophoblast begins to secrete chorionic gonadotrophin in very rapidly increasing amounts; this maintains the corpus luteum whose secretion of the sex steroids maintains the development of the uterine blood supply, and of the myometrium and of the decidua, and its function is reflected in the urinary pregnanediol and estrogens. Moreover, when sometime in the late second month or in the third month the amount of sex steroids supplied by the corpus luteum is no longer

adequate to maintain the uterine development, i.e., the uterine environment required by the developing fertilized ovum and demanded by it through its secretion of chorionic gonadotrophin, the placenta, at first gradually and later completely, takes over the secretion of the sex steroids and the corpus luteum atrophies. Further evidence that this is the sequence of events was produced by Browne and Venning,³¹ who showed that the administration of large amounts of chorionic gonadotrophin beginning just after ovulation and continued till menstruation did three things: it delayed menstruation in proportion to the amount of hormone given, it increased the pregnanediol output, and it produced a decidual reaction in the uterus. Therefore we may conclude that the maternal uterine environment in all its components—its blood supply, its myometrial, and, more obviously important, its decidual development—is completely dependent, from the moment of implantation, upon the maternal corpus luteum's ability to respond to demands made upon it by fetal tissues developing within the uterus. In other words, the maternal uterine environment is not a sort of prefabricated dwelling arbitrarily provided by the mother in which the fertilized ovum must develop; it is the work of a partnership between the fetal trophoblast and the maternal corpus luteum and the active partner is the trophoblast.

This does not mean that the fetus cannot be reached and harmed by extrauterine maternal environmental factors such as rubella, intoxications, nutritional defects, radiation, and so forth. No doubt it can be adversely affected by them, but far from being the common and usual causes of abnormality and abortion they are uncommon and even rare. On the other hand, it seems to be true that if the fertilized ovum is normal, it will make normal demands upon the mother who will provide the environment it requires for normal development. If the fertilized ovum is not normal, it cannot make normal demands upon the mother, and the abnormal demand is made apparent in a low titer of chorionic gonadotrophin in early pregnancy, while the abnormal response is inevitable and is seen in a low pregnanediol output. The end is generally abortion at some stage, usually, but not always, an early one.

If the fertilized ovum is not normal and it has not been made abnormal by the uterine environment, the original defect must have come from one or both of the germ cells. Vara and Pesonen³² have reported the finding of ova in human ovaries which carry abnormal chromosome systems and there is other evidence^{33, 34} pointing to the existence of abnormal ova. That approximately 10 per cent of spermatozoa are morphologically abnormal is well known and if this percentage exceeds 20 or 25 per cent the donor is usually sterile. This, to me, suggests, not that a morphologically abnormal sperm unites with a normal ovum, but that when a high percentage of morphological abnormality is present the remaining apparently normal spermatozoa must be abnormal functionally.

We know that many ova develop abnormally after fertilization for we see them as early abnormal abortuses, but there are many others which perish at such early stages of their development that under normal conditions we have no opportunity of seeing them or recognizing their abnormality.

Between 1942 and 1949, Hertig and Rock,³⁵⁻³⁸ to whose most important studies we owe our knowledge of the earliest stages of human development, collected 28 early fertilized ova from 136 women, all before the first missed period. These women all had pelvic disease requiring operation and, while awaiting operation, coitus was timed with a view to conception. In each the coital history was known; each woman had had an average of 4.5 living children and only an average number of abortions. Of the 28 ova so discovered, 12 were definitely abnormal. Four were very early and had not embedded; they were so abnormal that it was felt that they were incapable of embedding.

Three had embedded but were so abnormal that they would probably have been expelled with little or no delay of the next menstruation. These 7, or 25 per cent, of the 28 ova discovered would probably have caused at most a slightly delayed "period" with perhaps some increase of bleeding and pain. The remaining 5 abnormal ova probably would have given rise to clinical abortions. So we see that 43 per cent of these 28 ova were abnormal, and in every case the abnormal ovum was developing abnormally in a decidual environment which, by every test that could be applied to it, appeared to be normal.

In 1921, Robinson³⁹ reported a study of reproduction in ferrets, which, like other animals with two uteri and multiple births, do not abort, but their ova that die early are absorbed and those which die later are mummified, as is occasionally seen when a fetus papyraceous is found in human multiple pregnancy. He determined the number of ova released from the ovaries of each animal by counting the corpora lutea and comparing their number to the number of fetuses found in the uteri, and discovered a wastage or prenatal death rate of 35 per cent. Some ova had been incapable of union with spermatozoa, others had been absorbed very early, others were in various stages of absorption and of mummification and were found between two ova that were developing normally on either side of them. He was unable to find any uterine abnormality by any known criterion. He concluded from his own study and from reference to similar work that, in mammals, a certain prenatal death rate is "normal and inevitable."

A most comprehensive and beautiful study of this sort was reported in 1923 by Corner^{40, 41} and concerned itself with reproduction in the domestic sow. He found that approximately one third of the sow's ova were lost. Some failed to unite with spermatozoa that had reached them, others failed to implant, and others were absorbed or became mummified at later stages.

In 1953, he and Bartelmez⁴² found the same order of prenatal death in *Macacus rhesus*. In discussing their work, Gibson⁴³ reported finding 2 very early abnormal baboon ova out of 6 that she had studied. At the same time, Hertig⁴⁴ brought his and Rock's figures up to date; they had by that time found 8 further ova from 30 more women with histories similar to those already reported upon, and 40 per cent of the total series of 36 ova from 166 women were abnormal. Hartmann⁴⁵ at the same time reported the finding of evidence of degeneration in a two-celled rat ovum. He believed that the best evidence of the ovular origin of prenatal abnormality and death is to be found in marsupials where there is no implantation, the ova lie free in the uterus, and a similar large proportion of them are lost. Such abnormal ova, he says, are "common to all animals, from sea urchins to mammals." Cassida⁴⁶ also has found a prenatal loss of ova amounting to over 40 per cent in rabbits and to 32 per cent in swine, while in a herd of subfertile cows, the total loss of ova amounted to 59.4 per cent as compared to an estimated prenatal loss of 30 per cent in normal cows. This and much other evidence leads to the conclusion that at least one third of all mammalian ova exposed to fertilization are or become abnormal, and that the fault cannot be in the maternal uterine environment; nor, since prenatal death is three times as common as human abortion, can it be attributed to the extra-uterine maternal factors that are known in rather rare instances to have an adverse effect on intrauterine development.

In 1944, Corner²⁵ reviewed the question of the prenatal wastage of ova that occurs in so many mammalian species, including man, and presented evidence for his belief that the principal cause of this great reproductive loss must be sought in genetic defects in one or both of the germ cells. In 1953, Corner and Bartelmez⁴² stated that there is ample evidence for believing that the inheritance of lethal factors adequately explains the prenatal loss of approximately

one third of fertilized mammalian ova which has been shown to occur. It is also well known that many of the minor and major congenital anomalies of human fetuses can be inherited.

The available evidence therefore favors the view that fetal abnormality and abortion are chiefly attributable to inherited detrimental or lethal characteristics, leading to structural or functional changes incompatible with normal development or with life. That this view is valid is not gainsaid by the fact that similar effects leading to abnormalities incompatible with normal development or with life may be much less frequently brought about by extra-uterine environmental factors.

If the majority of early spontaneous abortions are due to genetic causes inherent in defective germ cells, is the same true of the abortions that occur between the end of the first trimester and the period of viability? There appears to be no reason for thinking that it is not. Admittedly, many abortuses of this group are grossly normal and some of the later ones are born alive and the whole group resembles early premature labors more than it does the early group of abortions. It is also true that, since they occur at a time when abortion is not usually expected, not many endocrine studies have been done on these cases and not as much is known of the functional state of the trophoblast. It is also possible that some fault in the physiological control of the uterine muscle may be responsible in some cases. The possibility of genetic causation cannot be excluded, however. We know that hemophilia and Huntington's chorea are inherited detrimental factors that do not show their effects until after birth and that the latter makes its appearance only in the third or four decade of life.

There appears to be much to support Streeter's⁴⁷ view that fertilized ova vary greatly in their inherent capacity for development and life. Some are so lacking in this vital capacity that they perish at any stage of uterine development, others are born alive but succumb at various ages, and yet others may live to extreme old age. He lays great emphasis on the functional capacity of the ovum for living and says that "a good egg is one that develops normally."

Recently Lilienfeld and Pasamanick⁴⁸ in an investigation of cerebral palsy and other postnatal conditions have found that the mothers of children so affected have had a higher reproductive loss than is found in the population as a whole. They believe this may be explained by the hypothesis of a "continuum of reproductive casualty" which has a "lethal component consisting of abortions, stillbirths, and neonatal deaths and a sublethal component" which, they think, may include cerebral palsy and other defects which arise in postnatal life. This is in agreement with Streeter's idea and their views combine with his to emphasize the probability that much of the reproductive loss at all stages from fertilization to birth and even in extrauterine life depends upon inherent defects in the fertilized ovum which originate in one or both of the germ cells.

If abortion is chiefly due to genetic factors, prognosis must always be guarded and treatment is of questionable value. The only abortion that may benefit from treatment is a threatened abortion and, as Mason⁴⁹ has so well said, "a threatened abortion may represent, not the beginning of trouble, but the end of a damaging process which is past help."

The actual number of threatened abortions is very hard to determine, but Randall and his co-workers⁵⁰ reported that 24 per cent of all pregnant women observed by them bled at some time in early pregnancy and 27.5 per cent of them actually aborted; that is, somewhere near 75 per cent of the women who bled in early pregnancy carried to term when left to themselves. Colvin⁵¹ reported that of 1,570 threatened abortions observed by his group,

69.9 per cent went to term with no treatment except routine vitamins. It is curious that 75 per cent is about the average rate of salvage of threatened abortion claimed by most of those who have published more or less enthusiastic reports of their success in its treatment with progesterone or estrogen and progesterone combined. The Smiths^{52, 53} hopes for stilbestrol as a possible means of limiting the frequency of abortion have not been substantiated by Ferguson⁵⁴ or by Dieckmann and his associates.⁵⁵

Most authorities hold that to be considered a habitual aborter a woman must have had 3 consecutive abortions. But Wall and Hertig⁵⁶ stated that a woman who has aborted once is a potential habitual aborter and the studies of pregnanediol output during pregnancy and of pregnanediol output and endometrial biopsies^{26, 27} between the pregnancies of women who have previously aborted once or more than once are strongly in favor of this view. It appears that their hope lies, as Colvin⁵⁷ says, in "persistence of effort." Robinson and Corner showed that in lower animals some individuals lose very few of their ova by prenatal death and others large or very large proportions of theirs. The same is manifestly true of women. It seems to be true that about all that can be done for them is to see that every effort has been made to ensure that they and their husbands are in the maximum of health before conception occurs and to hope that sooner or later by "persistence of effort" they will succeed in having a normal ovum fertilized by a normal spermatozoon. If they do, they will almost certainly succeed in having a normal baby at or near term.

Is there any place for therapy with estrogen and progesterone in proportions more or less similar to those of normal pregnancy at the stage when symptoms arise? If the embryo is normal and the placenta grows and secretes normally, there should be no symptom of abortion. If either or both are definitely abnormal, abortion is almost inevitable. If the embryo is normal and the placenta is slow in taking over the secretion of sex steroids from the corpus luteum, and such cases have been shown to occur,²⁶ a combination of estrogen and progesterone *may* help to carry such a patient over a critical time and so, since we cannot easily distinguish the very occasional case of this sort, we may be justified in using such therapy in a threatened abortion, but we are not justified in predicting a favorable outcome of the treatment or in attributing a favorable result to it.

Conclusions

Finally, it seems reasonable to reach the following conclusions:

1. Spontaneous abortion in the great majority of cases is determined by genetic factors carried in the chromosomes of one or both of the germ cells.
2. The maternal uterine environment depends on the mother's ability to respond to normal stimuli arising in the fetal trophoblast; for such stimuli to be normal the trophoblast must be normal and this presupposes a normal ovum fertilized by a normal spermatozoon. If either germ cell is abnormal, the conceptus will be abnormal and will nearly always be aborted.
3. There are extrauterine environmental factors which may interfere with normal intrauterine development and lead to abnormalities of the fetus and to its death and expulsion, but they account for only a small proportion of abortions. That purely uterine factors can cause maldevelopment of a normal zygote and lead to its abortion seems improbable.
4. Treatment of abortion, whether as an isolated or a recurring event, seems to be of doubtful value, though it may be of use in a small minority of cases.

5. Human spontaneous abortion appears to be one aspect of the biological problem of prenatal death in mammals which is a part of the greater problem of reproductive wastage which we see in all living things. What its meaning is we cannot say. To the individuals whom it affects it is often a tragedy, but that it is "normal and inevitable," as Robinson said, and essentially conservative in its nature can scarcely be doubted.

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Original Reports

UTERINE CONTRACTILITY IN POLYHYDRAMNIOS AND THE EFFECTS OF WITHDRAWAL OF THE EXCESS OF AMNIOTIC FLUID*

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IT IS currently agreed^{9-12, 18, 20, 22, 24, 28, 31, 34, 38} that in polyhydramnios the overdistention of the myometrium increases the tonus of the uterus and reduces the force of the contractions. These alterations of uterine contractility are responsible for the slow progress of labor in this condition. Other disturbances of uterine contractility like spasms of the upper segment of the uterus^{34, 38} and of the cervix²¹ have also been described during the labor of a patient with polyhydramnios.

Both oxytocic^{24, 31} and "spasmolytic" drugs²¹ have been recommended as therapeutic measures, but the most used procedure is the artificial rupture of the membranes at the beginning^{11, 28} or in the middle^{10, 31} of the first stage of labor. It corrects overdistention, the contractility of the uterus improves,^{18, 34} and labor is accelerated.^{6, 12, 18, 21, 38} Barry⁷ prefers to withdraw the excess of fluid through abdominal puncture in order to avoid the dangers consequent upon rupture of the membranes, such as prolapse of the cord.

With the exception of Demelin¹⁸ and Yordan and D'Esopo,⁴⁴ observers believe that in polyhydramnios during the third stage of labor and the early puerperium, uterine contractility and tonus are reduced below normal values, leading to an increase of uterine hemorrhage during these periods. Many authors^{6, 7, 10, 12, 22, 34} consider this fact and the high incidence of prolonged labor as the consequences of a weakness of the myometrium.

Measurements of amniotic fluid pressure have been made by Wieloch⁴³ who found no intrauterine pressure in chronic polyhydramnios. Uranga Imaz and Gascon⁴² found 22 and 15 cm. of water pressure in the amniotic fluid in 2 cases; according to Rivett,³⁶⁻³⁷ the pressure of the amniotic fluid is surprisingly low. The only published record of amniotic fluid pressure in polyhydramnios is that of a case recorded by Bösch⁸ in which our recording methods were used.

The high incidence of premature labor,^{7, 21, 44} however, suggests that uterine activity may be prematurely increased in this condition.

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Withdrawal of the Excess of Amniotic Fluid.—During pregnancy withdrawal of fluid is used for the relief of the patient from mechanical disturbances. There is no agreement, however, whether this procedure will increase⁷ or reduce^{19, 23} uterine contractility or whether it will induce premature labor⁷ or facilitate the continuation of pregnancy.³⁶⁻³⁷ For such relief, abdominal puncture is preferred, whereas amniotomy through the cervix is considered more likely to induce labor.^{11, 19, 23, 28, 34}

Methods

Clinical Material.—Twenty-five patients with polyhydramnios were studied. In 6 of these patients the activity of the uterus was recorded several times in different stages of pregnancy, a total of 34 records was obtained. Six patients were primigravidas and 19 multigravidas. Only 3 cases were considered as subacute polyhydramnios and the remaining as chronic. The records were made between the twentieth and the fortieth weeks of pregnancy.

Recording of Uterine Activity.—The pressure of the amniotic fluid is recorded by means of a very thin polyethylene catheter (0.28 inside and 0.61 mm. outside diameter), introduced into the amniotic sac through the abdominal wall by means of an 18 gauge needle (Fig. 1). The needle is withdrawn after the catheter has been introduced. The other end of the catheter is connected to a Sanborn electromanometer and this with a Sanborn recording instrument.

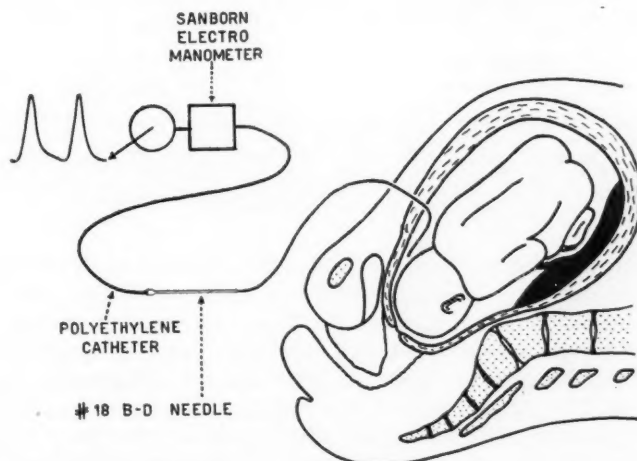


Fig. 1.—Method for studying the contractility of the uterus by means of the record of the pressure of the amniotic fluid (see the text for description).

The pressure of the amniotic fluid is a linear function of the tension of the uterine walls. As no significant shortening of the myometrium occurs during each contraction, the method can be considered as an isometric recording of the contractions of the uterus.

The *intensity* of each contraction is measured in millimeters of mercury by the increase it causes in the pressure of the amniotic fluid. In every record the average value for the intensity of the contractions is determined and shown at the bottom of the record (Fig. 4).

The *frequency* is expressed by the number of contractions every 10 minutes.

The *tonus* of the uterus is considered to be the lowest value of amniotic pressure recorded between contractions (Fig. 2). For measuring the tonus

it is necessary to have in all the records the same "zero" for the scale of pressure. We have adopted the level of the abdominal (intraperitoneal or extra-uterine) pressure as the "zero" of our scale. Measured from this zero, the amniotic fluid pressure is equal to the "pressure exerted by the uterus" on its contents, which is the pressure we want to determine. This pressure is equal to the difference between the amniotic (intrauterine) pressure and the abdominal (periuterine) pressure. The basis of the method for measuring the tonus is illustrated in Fig. 2. The method for determining the abdominal pressure has been previously described.¹³

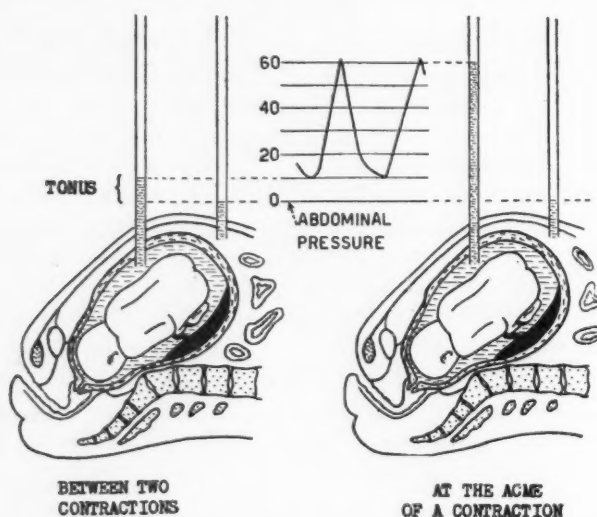


Fig. 2.—Basis for determining the zero of the scale of pressures. Two imaginary manometric tubes, connected to the amniotic cavity and the abdominal cavity, illustrate the level of the pressures in both compartments. The "pressure exerted by the uterus" on its contents is equal to the difference between the amniotic (intrauterine) pressure and the abdominal (periuterine) pressure. If the abdominal pressure is taken as the 0 of the scale, the amniotic pressure is equal to the "pressure exerted by the uterus."

Estimation of the Intrauterine Volume.—The fetus and the placenta were measured after delivery. The amniotic fluid was either withdrawn or estimated by the dye dilution method.³² The clinical dimensions of the uterus were also determined and correlated with the above-mentioned data.

The normal intrauterine volume at full-term pregnancy was estimated to be between 4 and 4½ L. The volume estimated for our cases of polyhydramnios are shown in Fig. 10 and for the most part fall between 6 and 8 L.

Withdrawal of the Excess of Amniotic Fluid.—This operation was performed 16 times during the recording of amniotic fluid pressure. Thirteen of these withdrawals were made by abdominal paracentesis and the remaining 3 by low artificial rupture of the membranes during labor. The amount of fluid withdrawn varied between 1 and 5 L.

Results

The value of the tonus and of the intensity of the contractions in polyhydramnios depends on two main factors:

1. The *overdistention* of the uterus as a result of the excess of amniotic fluid.
2. The *contractility* of the myometrium which may be "low," "high," or "intermediate." We consider low contractility to be that present in normal pregnancy before the thirtieth week; and high contractility that of a normal

labor. The effects of overdistention on the tonus and intensity of the contractions are completely different in a uterus with low and in a uterus with high contractility.

Influence of Overdistention of the Uterus on the Tonus and the Intensity of the Contractions in the Uterus With High Contractility.—Fig. 3 illustrates a case of polyhydramnios in a uterus with high contractility. The overdistention of the uterus (7 L.) raises the tonus to 25 mm. Hg and reduces the intensity of the contractions to 19 mm. Hg. Two liters of amniotic fluid are withdrawn in 2 stages of 1 liter each. These withdrawals almost correct the overdistention and almost restore to normal the tonus, which decreases to 12 mm. Hg and the intensity which increases to 39 mm. Hg. One more liter should be withdrawn in order completely to restore normal values of uterine volume, uterine

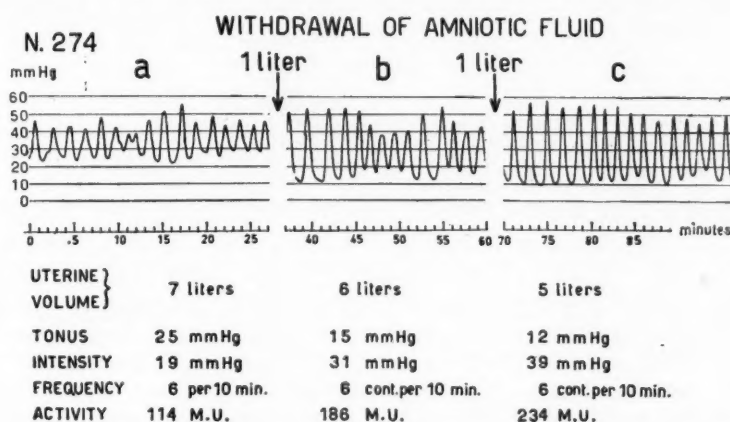


Fig. 3.—Withdrawal of the excess of the amniotic fluid in a case of polyhydramnios with high contractility (type 4). Record of the amniotic fluid pressures. At the beginning the uterus is overdistended (volume 7 L.), the tonus is very high (25 mm. Hg) and the contractions have a reduced intensity (19 mm. Hg). The withdrawal of fluid by abdominal paracentesis lowers the tonus and increases the intensity of the contractions. Labor was induced by this procedure. This case has a high contractility (type 4) in spite of being in only the thirty-fourth week of pregnancy.

contractions, and tonus. As a consequence of the withdrawal of fluid and of the increase in the intensity of the contractions, labor started some time after the withdrawal was finished. It should be emphasized that this uterus had a high contractility in spite of being in only the thirty-fourth week of pregnancy. This premature increase in contractility occurs very frequently in polyhydramnios.

A case of polyhydramnios recorded during spontaneous labor at full term is shown in Fig. 4. The overdistention of the uterus (which has a high contractility) raises the tonus and reduces the intensity of the contractions. As a consequence labor progresses very slowly. The artificial rupture of the membranes, which allows the escape of 1,100 ml. of amniotic fluid, partially corrects the overdistention and uterine contractility improves. The tonus decreases, the contractions become stronger, and labor progresses more rapidly.

The experiment shown in Fig. 4 is one of several proving that the cause of prolonged labor in polyhydramnios is overdistention which reduces the intensity of the contractions. In cases of polyhydramnios in which labor has started spontaneously, the uterine fibers are potentially able to perform strong contractions, equal to those of normal labor. But overdistention does not permit the fibers to produce these strong contractions. The correction of the overdistention by withdrawal of the excess of amniotic fluid increases the intensity of the contractions, and labor progresses at a normal rate.

We have not seen abnormalities during the third stage of labor or excessive bleeding which could be attributed to the weakness of the myometrium. We are convinced that if overdistention is corrected in due time, the myometrium will behave normally in polyhydramnios. This agrees with the clinical conclusions of Demelin¹⁸ and Yordan and D'Esopo.⁴⁴

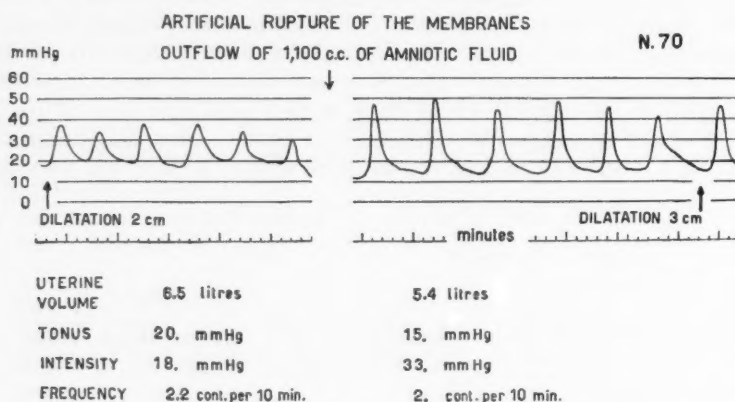


Fig. 4.—Effects of the artificial rupture of membranes in a case of polyhydramnios during spontaneous labor (full-term pregnancy). Record of the amniotic fluid pressure. The uterus is overdistended (volume 7 L.). The tonus is high and the contractions have a small intensity which is responsible for the slow progress of labor (cervical dilatation has reached only 2 cm. after 36 hours of labor). The artificial rupture of the membranes produces an outflow of 1,100 ml., partially correcting the overdistention. The tonus decreases, the contractions become stronger, and labor progresses more rapidly.

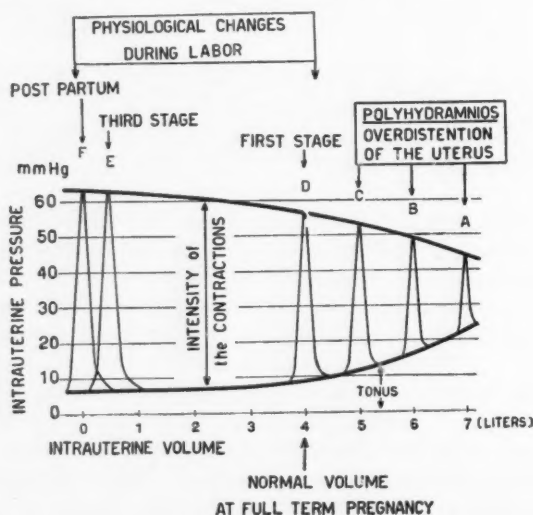


Fig. 5.—Effects of volume changes on the tonus and on the intensity of the contraction of a uterus with high contractility. This figure has been prepared with the results obtained in several cases. It represents schematically 6 uterine contractions (A-F) which illustrate the values of the tonus and of the intensity of the contractions for different uterine volumes ranging from 0 to 7 L.

The results we have obtained in the uterus with high contractility are illustrated schematically in Fig. 5. When the uterus has a normal volume, i.e., 4 L. in a full-term pregnancy, the tonus has an average value of about 10 mm. Hg, and the intensity of the contractions of about 45 mm. Hg. These values are illustrated by contraction D of Fig. 5.

When the volume of the uterus increases over normal values, the fibers are overdistended, producing an increase of the tonus and a reduction of the intensity of the contractions. For instance, if the uterine volume is 7 L., the tonus will rise nearly to 25 mm. Hg, and the intensity of the contractions will be reduced to 20 mm. Hg. If the excess of amniotic fluid is withdrawn, and overdistention is abolished, the tonus and the intensity of the contractions recover their normal values.

Influence of the Reduction in Uterine Volume During Delivery.—What happens when the volume of the uterus is reduced to less than 4 L., as occurs during normal labor when the fetus is expelled, is shown in the left half of Fig. 5. This problem has nothing to do with overdistention, but we consider it important to show the complete picture of the behavior of the uterus with high contractility when the volume of its content changes. Reduction of uterine volume to less than normal values produces less conspicuous changes than the overdistention. This fact proves that the uterus has a *great ability to adapt to reductions in its volume*.

What happens when the fetus has been delivered and only the placenta remains in the uterus is shown in contraction E of Fig. 5 which is in accord with previously reported results.⁵ Contraction F illustrates the result obtained after the placenta has been delivered and the uterus is almost empty. It can be seen that under both conditions the tonus is nearly as high as it had been when the intrauterine volume was 4 L.

The tonus of the puerperal uterus has obvious importance in the control of postpartum hemorrhage. The intensity of the contractions as measured by a small intrauterine balloon is even stronger after delivery than before. These contractions are also important during the third stage of labor, for by compressing the placenta they force blood to the newborn. They are essential also for expelling the placenta and during the puerperium for the expulsion of lochia and blood clots.

Differences Between the Uterus With Low Contractility and the Uterus With High Contractility.—In normal pregnancy the uterus has a low contractility during the first 30 weeks of pregnancy, a condition we have described as contractility, type 1. After the thirtieth week the contractility increases slowly and progressively, reaching its maximum value at the moment of the delivery of the fetus. After labor has started, we consider that the uterus has a high contractility which belongs to type 4. During the last week of pregnancy, uterine contractility increases progressively through types 2 and 3 which are intermediate between types 1 and 4 (see Fig. 11).

Three basic differences between type 1 and type 4 are schematically illustrated in Fig. 6 and are as follows:

1. *The intensity of the contractions.* When there is a normal volume (i.e., in the absence of overdistention), the uterus with high contractility (type 4) performs strong contractions with an average intensity of between 30 and 50 mm. Hg. On the contrary, the uterus with low contractility (type 1) performs weak contractions with an average intensity of between 2 and 7 mm. Hg.

2. *The tonus.* In the uterus with normal volume and high contractility, the tonus will be around 10 mm. Hg. If the uterus has a low contractility, the tonus will be around 5 mm. Hg.

3. *Effect of overdistention.* In the uterus with high contractility overdistention raises the tonus very much and greatly reduces the intensity of the contractions. These effects have been extensively described before. If the uterus has a low contractility, overdistention has a much smaller effect on the tonus and

on the intensity of the contractions; we can say that the uterus with low contractility has a greater distensibility or that it is much less affected by overdistention than the uterus with high contractility.

The record shown in Fig. 7 was obtained in a case of polyhydramnios with the uterus much overdistended (volume 7.5 L. in the twenty-first week of pregnancy) and with low contractility. The tracing shows the small value of the tonus and of the intensity of the contractions, and the very small effect of the withdrawal of a very large amount of amniotic fluid (5 L.). Fig. 7 should be compared with Figs. 3 and 4, which show records obtained in polyhydramnios with high contractility.

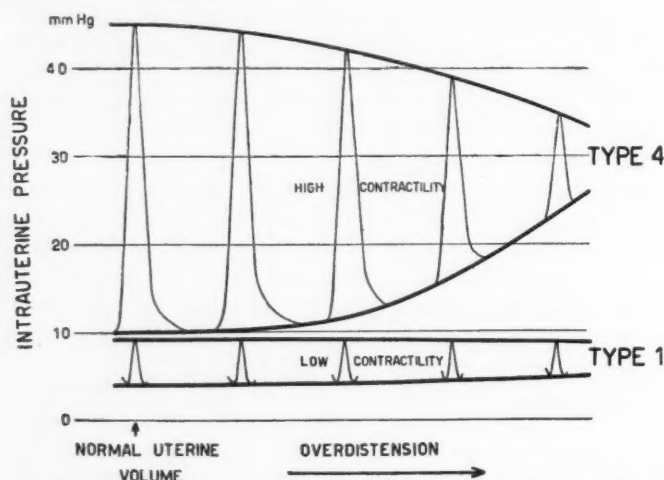


Fig. 6.—Different effects of overdistention in uterus with high and with low contractility. The uterus with low contractility has a low tonus (5 mm. Hg), performs small contractions (4 mm. Hg), and has a great capacity for adaptation to overdistention. The uterus with high contractility performs strong contractions (average to 40 mm. Hg), has a higher tonus (10 mm. Hg) and has less capacity for adaptation to overdistention, which produces a great increase in the tonus and reduction in the intensity of the contractions.

N.461

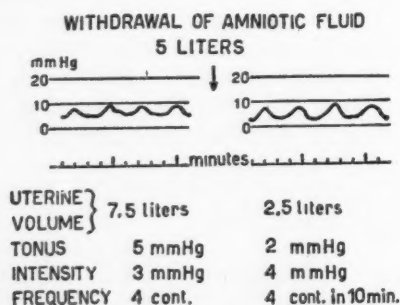


Fig. 7.—Polyhydramnios with low contractility (type 1). Record of amniotic fluid pressure obtained in the twenty-first week of pregnancy. Contractions are very small and the tonus is low (within normal values of pregnancy) in spite of the very large volume of the uterus. The withdrawal of 5 L. of amniotic fluid has very little effect on the tonus and on the contractions. This figure should be compared with Fig. 3 which represents a case of polyhydramnios with high contractility.

Classification of All the Cases of Polyhydramnios of This Series, According to the Contractility of the Uterus

For the sake of simplicity we consider only 4 types of uterine contractility. Type 1 corresponds to low contractility; type 4 to high contractility, and types 2 and 3 are intermediate types.

In order to facilitate the classification of the type of polyhydramnios, we use a graphic representation of the average values of the tonus and of the intensity of the contractions of each case, plotted against the volume of the uterus. Fig. 8 illustrates this method of representation. It has been prepared with the data obtained from Case 274 whose original tracing is shown in Fig. 3. The details of the method of representation are explained in the legend of Fig. 8: (1) The value of the tonus can be appreciated by the distance of the zero to the base of each vertical line. (2) The intensity of the contraction is shown by the height of each vertical line. (3) The 2 curved lines illustrate the effect of the withdrawal of the excess of fluid on the tonus and the intensity of the contractions.

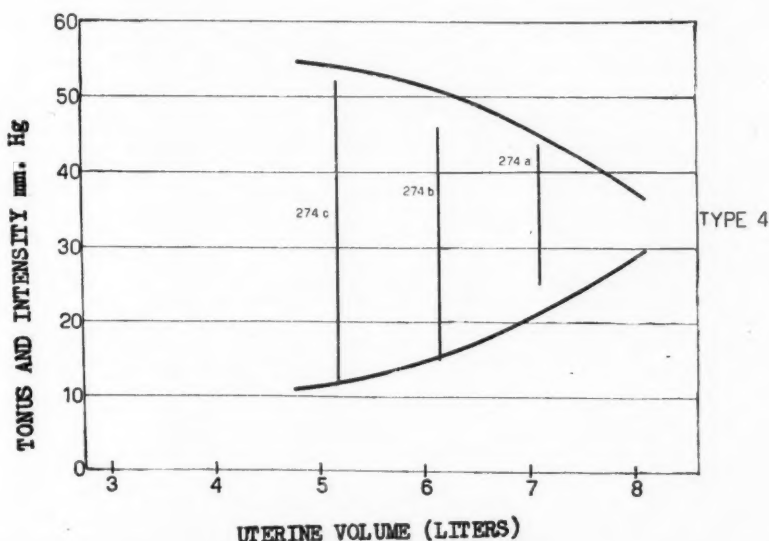


Fig. 8.—Graphic expression of the experiment shown in Fig. 3. The length of each vertical bar indicates the average intensity of the contractions. The lower end of the bar indicates the value for the tonus. The position of the bar in relation to the abscissa indicates the volume of the uterus. Bar 274a corresponds to the value obtained at the beginning of the record (uterine volume 7 L.). Bars 274b and 274c show the values after the withdrawal of amniotic fluid made in 2 stages of 1 L. each.

Case 274 is one of polyhydramnios with high contractility in which two withdrawals of amniotic fluid of 1 L. each were performed during the recording. This is the only case illustrated in Fig. 8. In Fig. 9, in addition to Case 274, two more cases are shown: (a) Case 206 with high contractility (type 3), whose original tracing is shown in Fig. 15; and Case 461, with low contractility (type 1), whose original record of amniotic fluid pressure is shown in Fig. 7.

The difference in the characteristics of uterine contractility of types 1, 3, and 4, and its behavior when the uterine volume is changed are clearly shown in Fig. 9. We wish to emphasize the great difference in the value of the tonus and of the intensity of the contractions between these 3 cases of polyhydramnios (Nos. 274, 206, and 461). The 3 cases, before withdrawal of any amniotic fluid, had had approximately the same uterine volume, i.e., between 7 and 8 L.

The value of the tonus and the intensity of the contractions of all the cases of polyhydramnios recorded by us are graphically illustrated in Fig. 10. As shown by the curves, these cases can be grouped in the 4 different types of contractility.

Fig. 9.

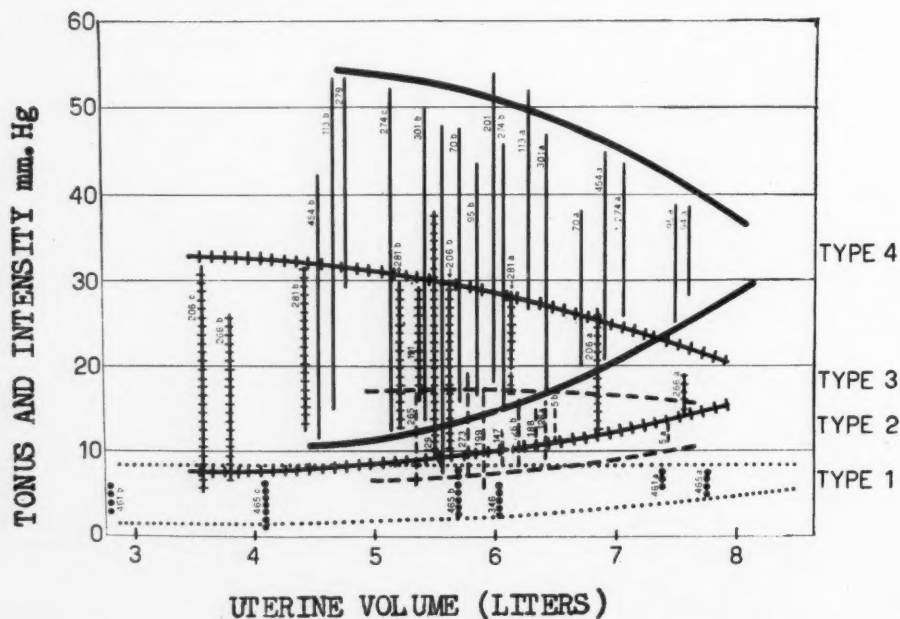
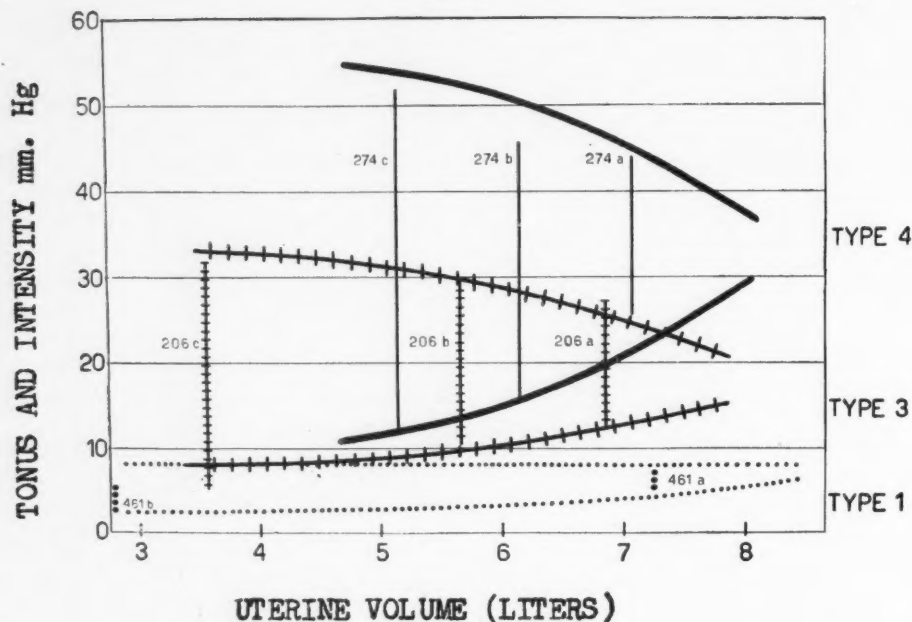


Fig. 10.

Fig. 9.—Different behavior of uteri with contractility types 1, 3, and 4. The same method of representation is used as in Fig. 8. Case 274 which belongs to type 4 and which was shown in Fig 8 is also included here. In addition, cases 206 (type 3) and 461 (type 1) are presented for comparison. The original records of Cases 206 and 461 are shown in Figs. 15 and 7, respectively.

Fig. 10.—Results of all the cases of polyhydramnios recorded. The same method of representation is used as in Figs. 8 and 9. The values for the tonus and for the intensity of the contractions of each record are plotted against the volume of the uterus. The curved lines group all the cases presenting the same type of contractility. The serial number of each case is indicated; when followed by *a* it corresponds to the record obtained before any withdrawal of amniotic fluid.

Premature Increase in Uterine Contractility in Polyhydramnios.—In normal pregnancy (Fig. 11) uterine contractility remains low until the thirtieth week. After that date it increases slowly and progressively, reaches type 2 around the thirty-seventh week, type 3 in the days before labor, and type 4 during established labor.

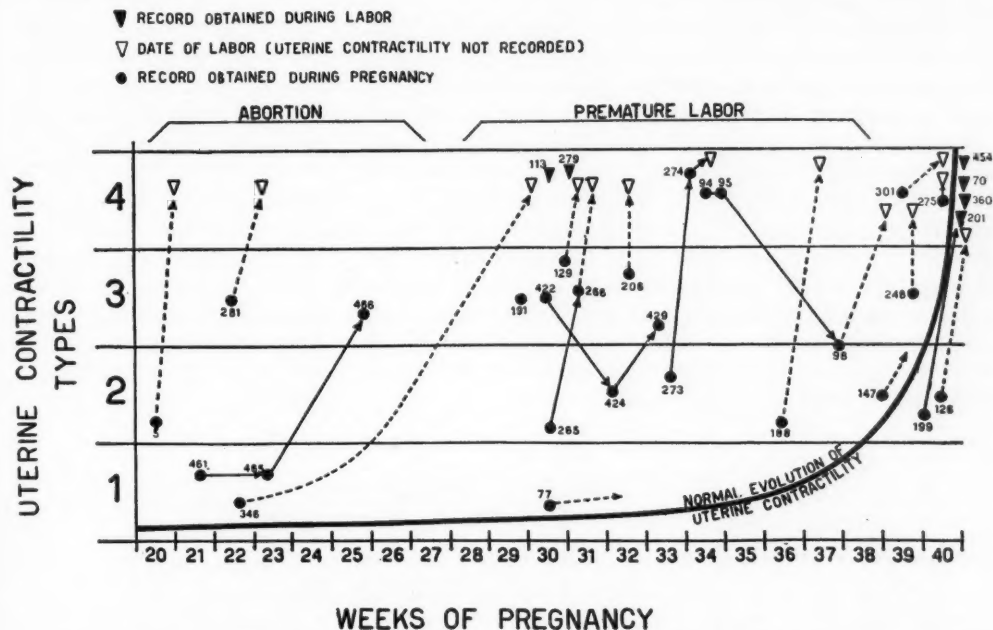


Fig. 11.—Premature increase in uterine contractility in polyhydramnios. The curved line indicates the normal evolution of contractility in pregnancy. The contractility of each record is plotted against the duration of pregnancy for all the cases we have recorded. Black circles indicate records made in polyhydramnios during pregnancy and black triangles during labor. White triangles indicate the date of delivery in cases in which uterine contractility was not recorded during labor. (It is assumed that uterine contractility during labor always belongs to type 4.)

Full lines connect different records obtained from the same patient in different periods of pregnancy and indicate the evolution of the contractility of that case. Dotted lines indicate supposed evolution of the contractility in cases in which uterine contractility was not recorded during labor.

In 60 per cent of the recorded cases of polyhydramnios, uterine contractility increases prematurely and reaches types 3 and 4 long before the term of pregnancy. As a consequence, in approximately 60 per cent of the cases of polyhydramnios there is a contractility higher than that of a normal pregnancy of the same duration. This ratio increases to nearly 80 per cent if the cases recorded after the thirty-eighth week of pregnancy are excluded. An example of this premature increase of contractility is the already discussed Case 274 (Figs. 3 and 8) which at the thirty-fourth week of pregnancy exhibited a high contractility (type 4).

Record 273 was obtained in the same case, four days before record 274. When record 273 was obtained, the uterine volume was 5.8 L. and uterine contractility was of type 2 (Fig. 12). In 4 days the uterine volume increased 1.2 L., reaching 7 L., and the contractility also increased very much, becoming of type 4. This rapid progress of uterine contractility is frequently seen in polyhydramnios as can be observed in Fig. 11.

Premature Labor and Abortion in Polyhydramnios.—The date of spontaneous labor or abortion is known in 21 of our 25 cases. Two of the 21 patients had a spontaneous abortion and 8 had spontaneous premature labor.

This means that in 10 of the 21 cases, i.e., 47 per cent, pregnancy was spontaneously interrupted before term.

The high incidence of premature labor in polyhydramnios can be easily explained in view of the premature increase of uterine contractility which occurs in this condition. The cause of the premature increase of uterine activity will be discussed farther on.

There seems to exist a contradiction between the 2 following facts which have been previously stated: (a) During pregnancy in cases of polyhydramnios there is a contractility higher than that of a normal pregnancy of the same duration. (b) During labor the contractions in polyhydramnios are weaker than normal and this weakness is responsible for the slow progress of parturition.

There is no actual contradiction, however. In polyhydramnios uterine contractility increases prematurely and reaches the characteristics of high contractility much before the term of pregnancy. This high contractility is more or less masked by overdistention, which reduces the intensity of the contractions, at times preventing the commencement of labor, at others slowing down its progress. If the overdistention is corrected, the uterus displays its ability to perform strong contractions and labor will start. If labor is already started, its progress will be accelerated.

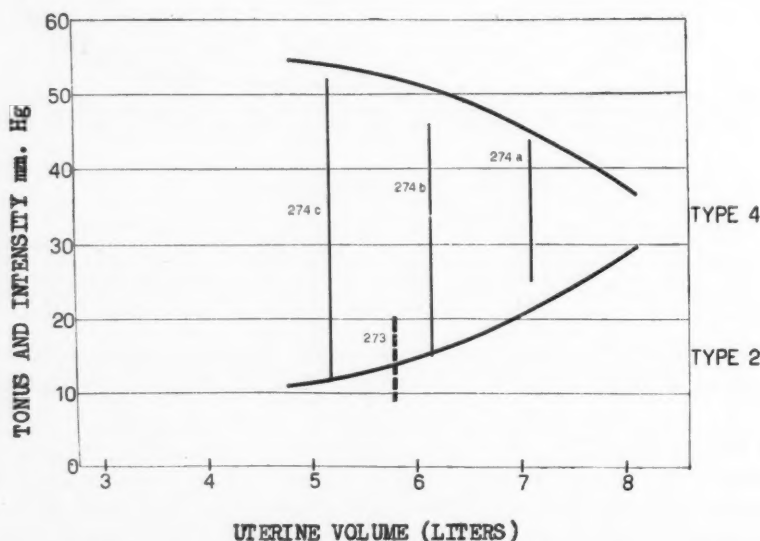


Fig. 12.—Rapid increase in uterine contractility in one case of polyhydramnios. The same method of representation is used as in Figs. 8, 9, and 10. Record 273 was obtained on the same patient 4 days before record 274.

Hypothesis for the Explanation of the Premature Increase in Uterine Contractility in Polyhydramnios

In a normal pregnancy with low contractility the intravenous injection of oxytocin at a rate of 10 miliunits per minute will change the characteristics of low contractility into those of high. In other words it will increase the intensity of the contractions and the tonus, and reduce the distensibility of the uterus.¹⁴

This is one of the several facts supporting the hypothesis that the increase in contractility which occurs in the last part of normal pregnancy is caused by an increase in the secretion rate of oxytocin by the neurohypophysis.

Other facts supporting this hypothesis have been previously published.^{15, 16} This hypothesis is in part based on the work of Ferguson²⁵ who has proved in several animal species that distention of the genital tract reflexly increases the secretion of oxytocin by the neurohypophysis.

In *normal pregnancy* the weight of the uterus does not increase significantly after the thirtieth week (Fig. 13) and as the fetus continues to grow very rapidly, the uterine wall is progressively distended.²⁶ This distention should produce, according to Ferguson, a progressive increase in the rate of secretion of oxytocin and consequently a similar increase in the contractility of the uterus. In this way we can explain the progressive increase in uterine contractility occurring during the last weeks of normal pregnancy as shown in Fig. 11.

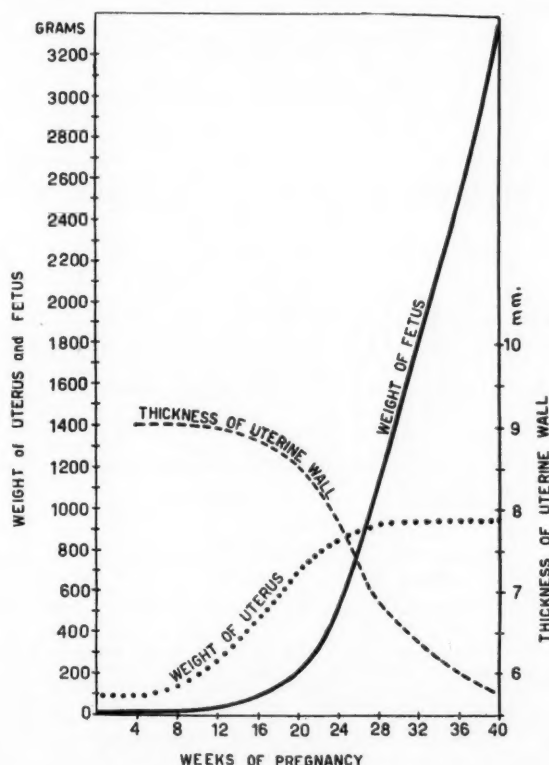


Fig. 13.—Distention of the uterine wall in the last part of normal pregnancy. The weight of the uterus, the weight of the fetus, and the thickness of the uterine walls are plotted against the duration of pregnancy. (Modified from Fig. 5 of Gillespie.²⁶)

When the contractions of the uterus become strong enough to start opening the cervix, labor will begin. The distention of the uterine cervix is a very strong stimulus for the reflex secretion of oxytocin.²⁵ A cycle is thus started because the uterine contractions produce the distention of the cervix, which reflexly increases the secretion of oxytocin, which in turn increases more the contractions of the uterus.

In polyhydramnios, there is a premature increase in the volume of the uterus which produces premature distention of the uterine walls. This distention stimulates the secretion of oxytocin by the neurohypophysis, which may explain the premature increase of uterine contractility which so frequently occurs in this disorder.

Consequences of the Overdistention of the Uterus on the Intensity of the Contractions.—The overdistention has two opposite effects on uterine contractility in polyhydramnios: (1) reflexly, through the neurohypophysis, it increases the secretion of oxytocin and increases the uterine contractility; (2) directly on the uterus it reduces the intensity of the contractions although it raises the tonus.

The value of the intensity of the contractions in each case of polyhydramnios will depend on the equilibrium between both effects.

The Effect of the Withdrawal of Fluid.—The withdrawal of the excess of amniotic fluid is usually performed for the relief of the patient. It is very important to know whether this withdrawal of fluid will induce labor or will favor the continuation of pregnancy.

N. 465

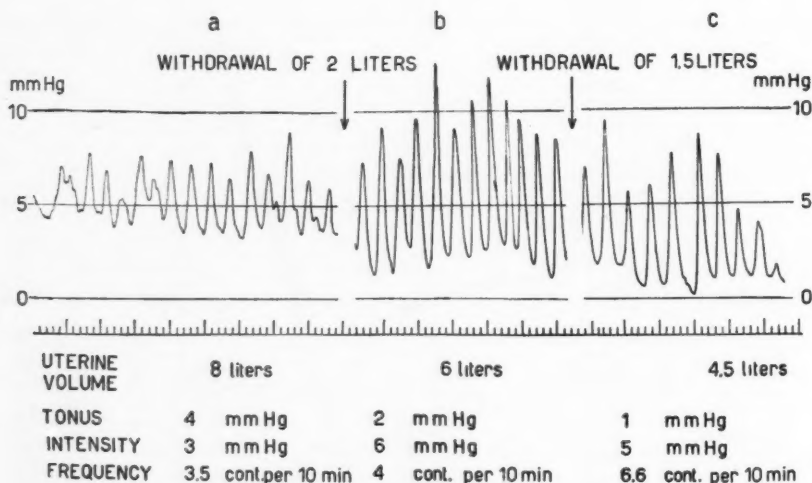


Fig. 14.—Effect of withdrawal of the excess of amniotic fluid in a case of polyhydramnios with low contractility (type 1). Record of amniotic fluid pressure obtained in the twenty-third week of pregnancy. Immediately after the first withdrawal of fluid the tonus decreases and the contractions increase their intensity, but do not become strong enough to be able to start labor. After that, the intensity of the contractions diminishes progressively. Labor is not induced and pregnancy continues. This experiment is schematically illustrated in Fig. 16, type 1.

This record was obtained from the same patient as record 461 shown in Fig. 7. The contractions have similar intensity in both records; even so, they look much stronger in this record (465) because the electromanometer is working with higher amplification.

According to our results, the withdrawal of the excess of fluid will induce labor if the uterus has a high contractility (Figs. 3 and 15); and will not induce labor if the uterus has a low contractility (Figs. 7 and 14).

From a clinical point of view the uterus with high contractility can be easily recognized in a case of polyhydramnios because the tonus is higher than normal, whereas with low contractility the tonus is normal, even if the uterine volume is exceedingly large. Examples of these conditions are Cases 461 and 465 (Figs. 7 and 14).

Partial evacuation of the fluid is less likely to induce labor than the total withdrawal of the excess of the amniotic fluid.

Hypothesis for the Explanation of the Effect of the Withdrawal of the Excess of Fluid

The correction of the overdistention of the uterus in polyhydramnios has two effects:

1. *Acting directly on the uterus* it increases the intensity of the contractions by improving the mechanical conditions. The uterine fibers become shorter, the wall becomes thicker, and the inner surface area of the uterus is reduced. The increase in the intensity of the contractions is more evident the higher the contractility of the uterus. The withdrawal of fluid has much more effect on a uterus with high contractility (type 4) than on one with low contractility (type 1), as is illustrated in Fig. 16.

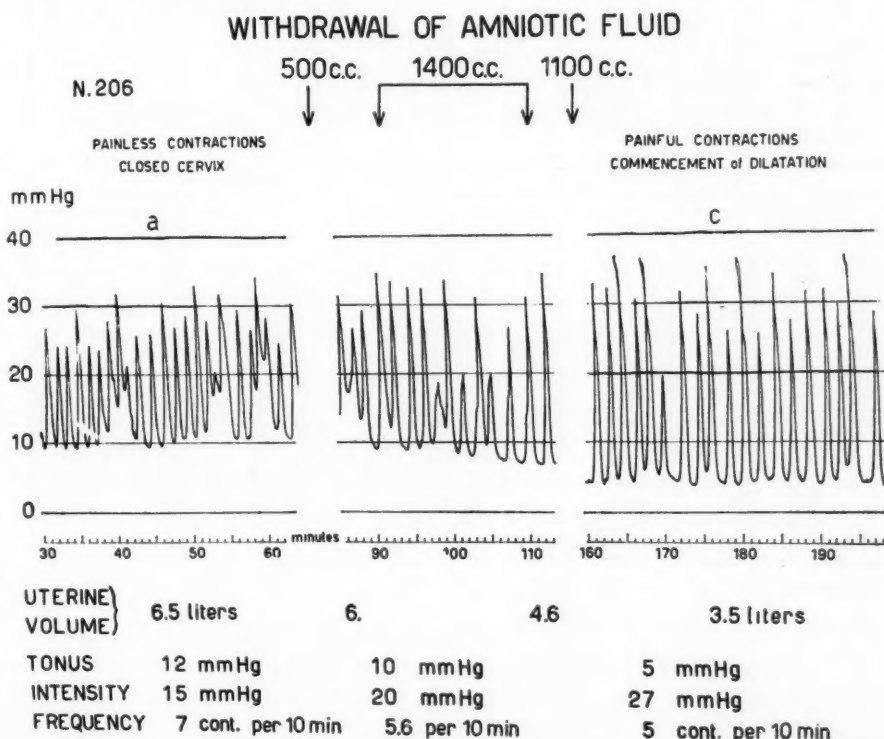


Fig. 15.—Induction of labor by withdrawal of the excess of amniotic fluid in a case of polyhydramnios with uterine contractility type 3. Record of amniotic fluid pressure obtained in the thirty-second week of pregnancy. The withdrawal of 3 L. of amniotic fluid by abdominal paracentesis produces a great increase in the intensity of the contractions which become strong enough for starting labor. As cervical dilatation progresses, the contractions continue to increase their intensity (not shown in the figure). This experiment is schematically illustrated in Fig. 16, contractility type 3.

2. *Indirectly*, the correction of the overdistention reduces the reflex stimulus on the neurohypophysis and consequently the secretion of oxytocin. The level of oxytocin in the blood diminishes *slowly* as oxytocin is cleared from the blood.

This indirect effect is predominant in the uterus with low contractility (Figs. 14 and 16). If the uterus has a high contractility (type 3 or 4), we assume that the blood level of oxytocin is high. Labor has not started spontaneously because the overdistention reduces the intensity of the contractions.

The withdrawal of the excess of fluid corrects the overdistention and by direct action on the uterus immediately increases the intensity of the contractions. These become strong enough to start the dilatation of the cervix. The cycle of labor is started and the consequences will be a progressive increase in the blood level of oxytocin and in uterine contractility, which will not stop until the delivery of the fetus (Fig. 16).

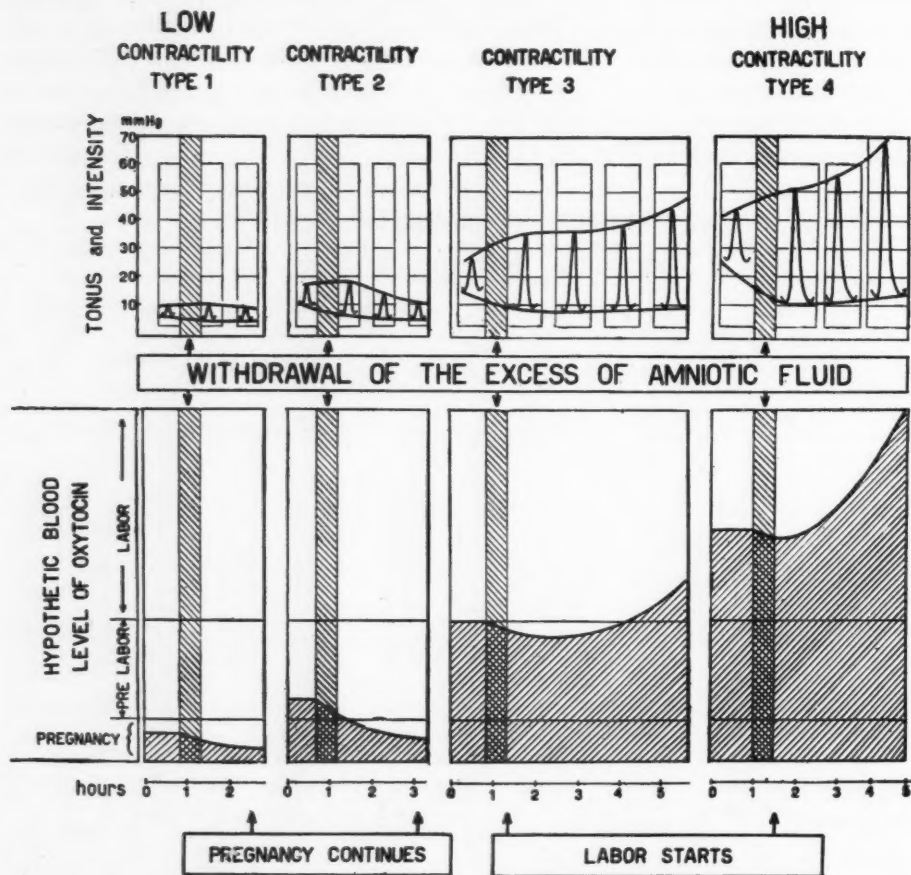


Fig. 16.—Schematic representation of the effects of the withdrawal of the excess of amniotic fluid in different types of polyhydramnios. In the upper part of the figure the tonus and the intensity of the contractions are represented. The changes produced by the withdrawal of fluid are illustrated by the curved lines. Short pieces of amniotic fluid records (containing one contraction each) are superimposed. The timing of each experiment, in hours, is shown at the bottom of the figure. The shaded area in the lower half represents the *hypothetic* level of oxytocin of the blood, according to our interpretation.

It should be emphasized that in polyhydramnios with high contractility, the withdrawal of fluid will remove the stimulus to the neurohypophysis to secrete oxytocin, but as the contractions *immediately* become strong enough to start opening the cervix, the distention of the cervix constitutes a new and stronger stimulus which may even increase the secretion of oxytocin by the neurohypophysis.

The induction of labor by withdrawal of fluid in 2 cases of polyhydramnios with high contractility is illustrated in Figs. 3 and 15. On the other hand Figs. 7 and 14 illustrate 2 cases in which the withdrawal of fluid did not induce labor, because in both cases the uterus had a low contractility. In Fig. 14 can be seen the immediate reduction in tonus and increase in the intensity

of the contractions produced by the first withdrawal of fluid. This is followed by a slow decrease in the intensity of the contractions, which we consider to be produced by a fall in the blood level of oxytocin. This interpretation is schematically shown in section 2 of Fig. 16.

Summary

In 25 cases of polyhydramnios the contractility of the uterus has been studied by recording the amniotic fluid pressure.

The value of the tonus and of the intensity of the contractions in polyhydramnios depends on two main factors:

1. The overdistention of the uterus raises the tonus and reduces the intensity of the contractions.
2. The contractility of the uterus in many cases increases prematurely and reaches labor values too early in pregnancy. This is the cause of the high incidence of premature labor in polyhydramnios.

During labor in cases of polyhydramnios, the uterine fibers are able to contract as strongly as in normal cases. Yet, due to the overdistention of the uterus, the contractions are reduced in their intensity and labor progresses slowly. This is the main cause of prolonged labor in this condition. Correction of the overdistention by withdrawal of the excess of fluid will make uterine contractility normal and will accelerate the progress of labor.

The withdrawal of the excess of fluid by abdominal puncture in cases of polyhydramnios with high contractility will induce labor. In cases with low contractility, pregnancy will probably continue after the withdrawal of fluid.

Hypotheses are presented to explain these observations.

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HUMAN BODY HAIR—A QUANTITATIVE STUDY

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A VARYING degree of hypertrichosis is a common clinical finding in women of the active reproductive age. Debarring rare cases where pathological lesion in ovary or adrenal is found, no definite factors can be implicated as causal agents in the large majority of such women. Attempts have been made, however, to establish causal relationship with a disturbance of endocrine function in this large group of cases of "idiopathic" hirsutism but it is only recently that a number of investigators^{5, 8, 10} presented biochemical evidence of a probable abnormal adrenocortical function. Among these authors Jailer and Vander Wiele⁸ are perhaps the only ones who had a large series of cases and they were unable to demonstrate steroid abnormality in the large majority of their patients. These authors rightly commented on the difficulty of defining the term hirsutism and it is possible that some of the cases studied may have had hair growth comparable to that in the higher range of normal variation. The present study was instituted with the primary object of elaborating a method of measuring body hair quantitatively, with a hope that this might enable the clinician to distinguish hirsute women in whom detailed endocrine work-up was indicated. Such a method would also allow comparison of normal hair growth in various ethnic groups and might be of considerable value in elucidating any striking inherited differences in the distribution and the pattern of hair growth if applied to different endogamous groups of India¹³ or elsewhere.

Perusal of the literature disclosed that few studies have been made of the quantitative estimation of body hair. The pioneer study of body hair conducted by Trotter and Danforth^{2, 3, 15} has been followed by the recent investigations of Pedersen,¹¹ Dupertuis and associates,⁴ Beek,¹ and Garn.⁶ These investigations have developed standardized methods for rating coarse or terminal hair, both directly and from photographs. It is necessary to state that the ratings done by these workers were on certain specified areas and the criterion employed was the presence or absence of terminal hair on these regions, with the only exception perhaps of Garn, who tried to quantitate the body hair. For this Garn devised a rating system based on the density of hair which varied on a scale of 0-4 on each region. He also determined a minimum number of hair regions, which should be studied separately, defining a region as an area of the body where hair growth is, at least, partially independent from

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that of neighboring regions. The ratings were made directly on nude subjects and at a standard viewing distance of 10 feet and under 150 foot lamberts of illumination. Garn thus rated 239 adult white men to determine whether a given individual was glabrous or relatively hairy.

The data presented here represent our efforts to measure quantitatively body hair in women supposed to have more or abnormal hair on certain parts of the body. In the absence of standards by which one can judge what is normal variation of hair growth, a comparative study of hair growth in apparently nonhirsute women and men was also made. Such comparative data from the point of view of quantity of body hair, as far as we are aware, are made available perhaps for the first time.

Method and Material

The method used here is based on features from Garn's procedure but it is very much modified. The salient features of this method are:

1. Ratings were made directly on the subjects (only a small loin cloth was allowed) from the closest possible distance and under 1,500 watts of illumination.

2. The study considers only terminal hair of minimal 0.5 cm. in length.

3. The body was divided into nine regions (Fig. 1). The regions, upper arm and thigh, lower arm and leg were numbered separately, for these regions appeared to be fairly independent for hair growth. In view of the smallness of the ear, middigital, lumbosacral, and lower back regions compared to the other regions considered, they were excluded in this study. Thus the total area studied was almost the same as in Garn's investigation.

4. In order to have a better idea regarding the quantity of hair in each region, three factors, namely, the quality, density, and the proportion of the area of the region covered by hair, were taken into account. By quality was meant the thickness of hair and this was rated on a scale of 1-3 by palpation. The density was rated on a scale of 0-3 for each specified region; the absence of hair or the presence of a few hairs in any region was indicated by zero. When the growth was very dense, it was indicated by the figure 3 and the intermediate range was divided into 2. The total quantity of hair for a particular region was obtained by multiplying the numerals for quality, density, and the fraction of the area of the particular region covered by hair. For example, if on a lower arm of an individual, the quality of hair rated was 1, the density was 1, and the dorsal surface only was covered by hair, then the quantity of hair for the lower-arm region would be 1 by 1 by $\frac{1}{2} = 0.5$. For the sake of brevity a round number was taken for counting. The final numerical hair growth score, obtained by adding the respective numerals for the nine regions, was taken as a measure of body hair.

5. After the rating scale had been developed on a small pilot group, it was tested by two independent persons at the same time on 90 subjects. As their results were fairly comparable, the method was applied to the further 94 persons by the author alone.

6. In all, 184 persons were rated. Their distribution according to age is shown in Table I. They fall into three groups:

- (1) Women who came with complaints other than abnormal hairiness formed the group of nonhirsute women. There were 100 in all, ranging in age from 15 to 48 years, the mean age being 27.2 years.

(2) Women who were referred to us from several private clinics for abnormal or excessive hair growth constituted this group. There were 34 in all. Their ages ranged from 15 to 41 years, with a mean age of 22.2 years.

(3) Fifty men constituted this group, ranging from 20 to 53 years of age, with a mean age of 28 years. Most of them were the workers at the Indian Cancer Research Centre. A few, however, were close relatives of the hirsute women.

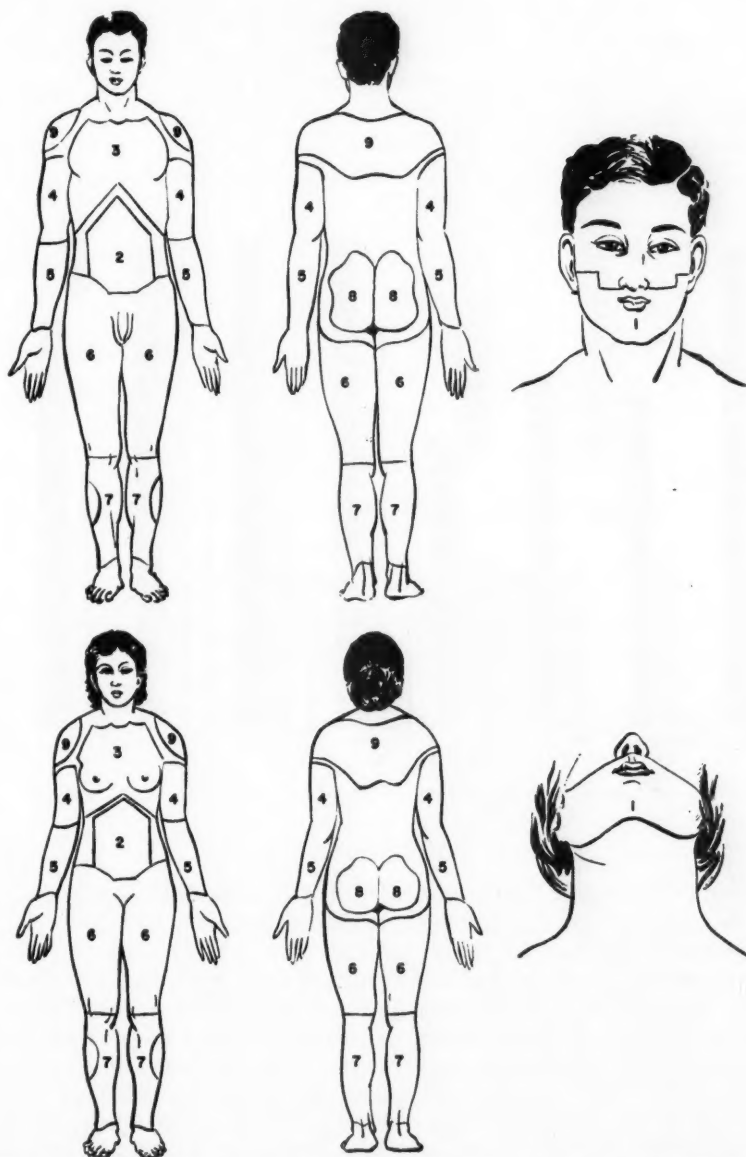


Fig. 1.—The body hair regions as defined in the text: (1) face, (2) abdomen, (3) chest, (4) upper arm, (5) lower arm, (6) thigh, (7) leg, (8) buttocks, (9) upper back.

It is important to state that, though the division of nonhirsute and hirsute women is only arbitrary, yet it is of significance because it is rare for a woman to be hairy and still not be concerned about her hair growth. Further questioning of the hirsute group of women regarding the motivation for visiting

a physician disclosed, in order of frequency, that (1) they or their relatives felt that such hair growth would jeopardize the possibility of marriage; (2) they thought they were changing sex; (3) the husbands had started to dislike them ever since they began to grow hair in certain regions; (4) they were interested in knowing whether investigation of them would help in preventing similar hair growth in their offspring who were then in the prepubertal age.

TABLE I. AGE INCIDENCE IN 184 SUBJECTS

	AGE GROUPS						TOTAL
	15-19	20-29	30-39	40-44	45-49	50-55	
Nonhirsute women	8	52	34	2	4	-	100
Hirsute women	7	20	6	1	-	-	34
Men	-	36	9	-	1	4	50

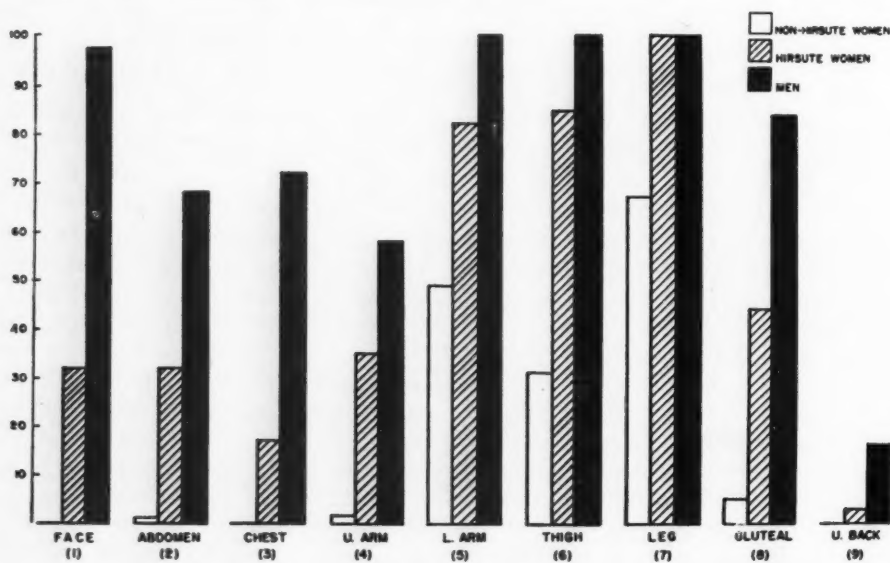


Fig. 2.—Frequency of appearance of terminal hair in specified regions.

Observations

Nonhirsute Women.—Thirty-one of 100 subjects had absence of terminal hair in all the regions studied by us. In the remaining 69 cases, as shown in Fig. 2, the commonest site for hair growth was the leg and in order of frequency the lower arm, thigh, buttocks, upper arm, and abdomen were found to have hair. It becomes evident from the histogram that in nonhirsute women, the presence of hair on the face, chest, and upper back is absolutely "unusual," while its presence on abdomen, upper arm, and buttocks is relatively "unusual." When the individuals were grouped from the point of view of the number of regions showing growth of hair, it was found that the large majority (93 per cent) did not show hair in more than three regions and, of the remaining 7, 6 showed it in four regions and 1 in five regions (Fig. 3).

During our study it was realized that the presence of hair on the leg, not necessarily in a measurable quantity, was a prerequisite for hair on other parts of the body. There were also marked variations in the proportion of the area covered by hair. By and large, the total quantity of growth of hair on the leg was more than that seen in other regions of the same individual. The growth

of hair on the thigh, though slight, was of measurable quantity in a small percentage of this group. The total hair growth score in the large majority (97 per cent), as shown in Fig. 4, did not exceed 7.

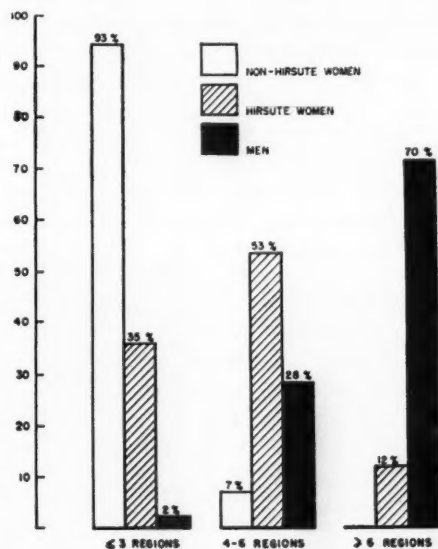


Fig. 3.—Growth of hair by number of regions.

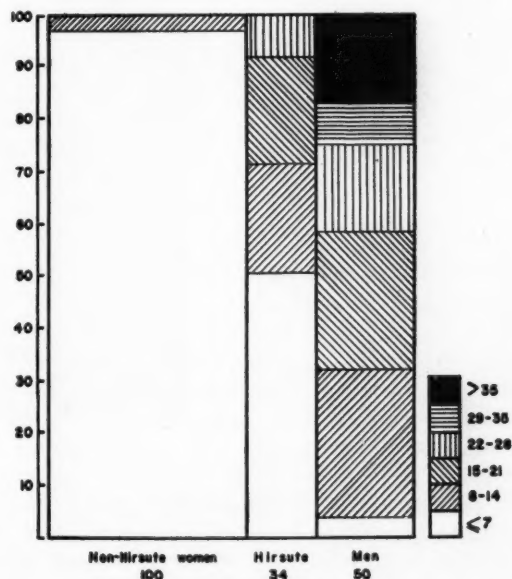


Fig. 4.—Frequency distribution of total amount of hair.

Hirsute Women.—All the 34 subjects had hair on the leg where hair was commonly found in the nonhirsute subjects; the difference, however, was in the quantity, more marked in most of the hirsute women. Unlike the non-hirsute ones, hair was found to be present in a measurable quantity on the thigh

in 29 and on the lower arm in 28 of 34 subjects. Along with the striking difference in the frequency of appearance of hair on the thigh, there was also an increase in all the three quantitative measures, viz., the quality, density, and the area covered by hair. The remaining regions in this order of frequency, buttocks, upper arm, face, abdomen, chest, and upper back, were found to have hair (Fig. 2). When the subjects were grouped from the point of view of the number of regions showing the growth of hair, the largest single group was the one showing 4 to 6 regions (Fig. 3). It is pertinent to mention that not a single subject showed growth of hair in all the "unusual" regions; the maximum number of such regions was 5 and the most uncommon regions in order of frequency were the chest and upper back. Regarding the density of hair in the "unusual" regions, it varied from person to person and in different regions of the same individual; for example, the hair on the chest ranged from circumareolar and sternal tuft to mat confluent with that of the region abdomen.

The total hair growth score varied from that seen in nonhirsute women to the score of 28. Although the total hair growth score in 17 of 34 hirsute women did not show any appreciable difference from that of the nonhirsute subjects, yet 6 of the 17 had a measurable quantity of hair on 1 to 2 "unusual" regions (Fig. 4). In the remaining 17 hirsute subjects, the total score in individual subjects bore no relation to the number of regions showing growth of hair nor had it anything to do with the selection of the "unusual" regions. In other words, two persons having similar hair growth score had a different number of regions showing growth of hair.

TOTAL AMOUNT	NO. OF "UNUSUAL" REGIONS							
	0	1	2	3	4	5	6	
0 - 7	11	4	2	-	-	-	-	
8 - 14	-	1	2	4	-	-	-	
15 - 21	-	-	2	3	2	-	-	
22 - 28	-	-	-	-	2	1	-	
29 - 35	-	-	-	-	-	-	-	
36 - 42	-	-	-	-	-	-	-	
43 - 56	-	-	-	-	-	-	-	

Fig. 5.—Number of "unusual" regions showing the growth of hair in 34 hirsute women.

From this study, selection of a group of women with considerable amount of hair growth was found to be practicable if, along with the total score, the number of "unusual" regions was taken into account. Arbitrarily, we selected subjects with a total score of 8 or above and more than two "unusual" regions, or with a total score of 15 or above and more than one "unusual" region to represent the abnormal group (Fig. 5). Thus 20 of the 34 women who originally complained of abnormal hair growth did not satisfy these criteria. In the remaining 14 women, it was interesting to note that there was a group of women who had hair on the face and other regions except the chest, and there was another group of women who had a considerable amount of hair on the chest and neck and other regions but the face (Figs. 6 and 7). A small group of women, however, had the combination of these two types. In these cases where there was familial hirsutism, it is interesting to note that the selection of region, namely, face or chest and neck, was identical in the female siblings who showed excessive hair growth.

Men.—All the 50 subjects had hair in the regions, lower arm, thigh, and leg. Seven of these had hair in all the nine regions while in one there was absence of hair in a measurable quantity on the face. The other regions represented in order of frequency were face, buttocks, chest, abdomen, upper arm, and upper back (Fig. 2). When individuals were grouped by the number of regions showing hair, the largest single group was the one that showed more than 6 regions (Fig. 3). The quality of the hair varied in different regions in the same individual and it seemed that, by and large, the hair on the lower extremity and chest was coarser than that seen on the upper extremity. The total hair growth score went from one extreme, amounting to that seen in the nonhirsute women, to the other extreme, showing profuse growth of hair amounting to a score of 54 (Fig. 4).



Fig. 6.



Fig. 7.

Comment

Besides age and sex,^{1, 12} and granting that humoral control of hair growth occurs, the final product of each individual follicle is largely dependent on genetically determined differences in the hair follicle itself.³ To substantiate this, there is a good body of evidence that there is no difference in the number of hair follicles per unit area on the face in men and women or between individuals of different races, yet there is certainly a difference in the extent and the degree of hair growth.¹⁴ For example, the classical hair growth in

women of the active reproductive age in Sweden¹¹ is limited to the scalp, eyebrows, eyelashes, axillary and pubic regions, and sometimes there is seen a slight hair growth in the nares, external orifices of the ears, and the perianal region. The pubic hair has a marked transverse limit and does not reach further than to the inguinal and genitofemoral folds. Hair growth outside these regions, according to Pedersen,¹¹ is regarded as hypertrichosis, provided the minimal length of the hair is 0.5 cm. According to this definition, hypertrichosis of the forearm or leg was seen in 60 per cent of Swedish women and of the breast in 35 per cent. In contrast to this group, of otherwise normal women of the United States 26.8 per cent had facial hypertrichosis,¹⁴ 35 per cent had more or less terminal hair on the trunk,³ and the extent of pubic hair was found to be what is described as "sagittal" in pattern in 10 per cent of normal white girls above the age of 19 years.⁴ As suggested by Beek,¹ it

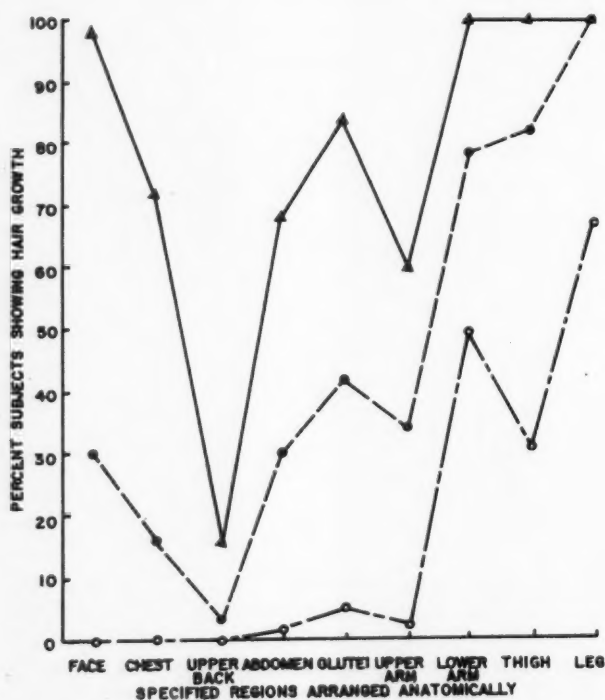


Fig. 8.—Nonhirsute women ○ ——— ○ ———
Hirsute women ● ——— ● ———
Men ▲ ——— ▲ ———

is conceivable that there are no typical male or female regions of hair growth but we feel that unless a reasonably accurate method for quantitative measurement of body hair is evolved, it is going to be difficult to draw a base line between a variation of normal and abnormal hair growth in women of various ethnic groups. In a study of extensive body surface such as this, the only way to assess roughly the weight of the body hair was to take into account the known variables for weight, viz., length, thickness, density, and the fraction of the area of the region covered by hair. In view of the fact that no two

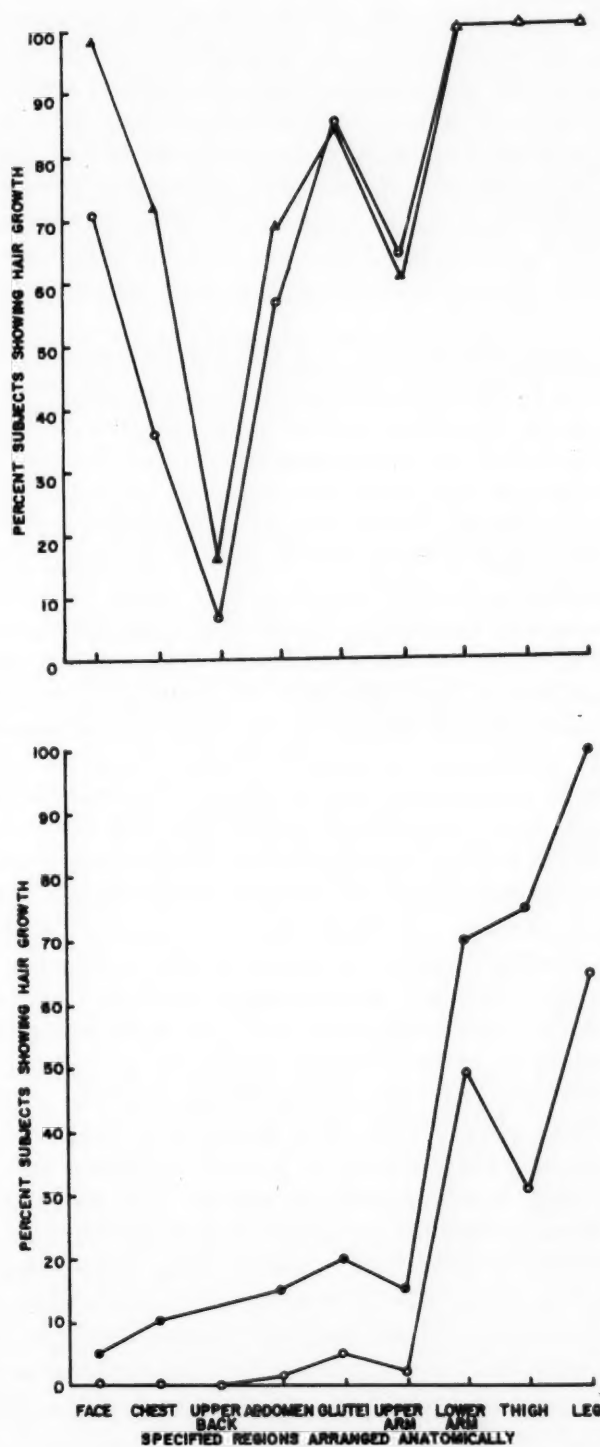


Fig. 9.—The lower part shows the pattern of curves seen in the nonhirsute and hypertrichotic women, while the upper demonstrates the similarity in pattern seen in the hirsute women and men.

adjacent hairs in any region are exactly similar in length, the presence of terminal hair of a minimum of 0.5 cm. in length was made obligatory for rating. In order to check critically the rough assessment made by this method and to give us a more accurate determination of body hair in the future, we are planning at present to employ a procedure similar to that described independently by Hamilton⁷ and Kinsell and associates.⁹ Obviously such a test is practicable in one or two regions in a few volunteers only. Finally, it is important to stress that although the observations recorded here are encouraging and suggestive, we need larger series of both the sexes to validate these initial findings.

The concept of the "unusual" regions in women derived from this study is only relative and is dependent on the difference in frequency of appearance of hair growth on the specified regions found between the two sexes. Such information can be of immense value if differentiation between normally hairy or hypertrichotic women and abnormally hairy or hirsute women be made out conveniently on such basis. When the distribution of subjects showing hair growth was plotted against the specified regions arranged anatomically, the curves of the nonhirsute women and men were found to be of different patterns, while the curve of the hirsute women was, roughly, the mean of the two with the exceptions that the face, chest, and thigh approximate much more closely the pattern seen in men (Fig. 8). We then felt that if we split up the group of the so-called hirsute women on the basis of two criteria, namely, the total hair growth score and the number of the "unusual" regions showing hair, we might be in a position to select a group of women for further investigation. Arbitrarily we selected individuals who had the total hair growth score of 8 (i.e., above the highest score found in nonhirsute women) or above, and more than 2 "unusual" regions (i.e., above the highest number of regions seen in nonhirsute women), or those having the score of 15 or above and more than one "unusual" region, to represent the abnormal group. Thus 20 of the 34 women who originally complained of abnormal hair growth did not satisfy these criteria. This difference was very well brought out when the frequency of appearance of body hair in specified regions of these two groups was compared with the standard curves obtained for the nonhirsute women and men, respectively (Fig. 9). In other words, 20 of the 34 subjects appeared to have body hair at a higher range of normal variation, i.e., hypertrichosis, and we may call them hairy but normal women. The curve of the remaining 14 constituting the so-called abnormal group had the male pattern and these may be called hirsute or abnormally hairy women. The latter group if subjected to detailed investigations may show some interesting findings. This does not mean that hypertrichosis may not require treatment for cosmetic or psychological reasons, but it does indicate that the problem is essentially that of controlling normal hair growth on any other part of the body.

Summary

1. An attempt is made to develop a practical method for quantitative measurement of body hair.

2. The importance of checking the observations obtained by this method on larger series should be emphasized. Such study will materially aid in an understanding of the normal variation in various ethnic groups or in endogenous groups in India or elsewhere.

3. The results of the investigation show that: (1) excessive amount of hair growth on the thigh is perhaps the first sign of developing hypertrichosis in women; (2) the method is found useful in differentiating hypertrichosis from abnormal hair growth in women and may also help to set up objective criteria to evaluate the effect of treatment on hair growth.

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**THE PROGNOSTIC SIGNIFICANCE OF GLANDULAR INVOLVEMENT
IN COLD KNIFE CONIZATION BIOPSIES IN CARCINOMA
IN SITU OF THE UTERINE CERVIX*†**

An Analysis of 136 Cases

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THE management of cancer of the uterine cervix, as carried out at the United States Naval Hospital, San Diego, California, was reported in detail in a previous publication.¹ Several recommendations for the treatment of noninvasive cervical cancer were endorsed as being the most universally accepted form of therapy at that time. No major change in the management of this condition has occurred at this hospital since our original report. It shall be the purpose of this study to report upon the clinical status of all patients treated in relation to the extent of the microscopic pathology in the pre-treatment conization biopsy and the residual pathology in the postoperative specimen. It shall also be the purpose of this study to analyze critically the methods used and to make specific recommendations for more definitive therapy if this is found to be indicated. We shall not attempt to review the voluminous literature on this subject but will confine our discussion entirely to noninvasive cancer of the uterine cervix from the standpoint of diagnosis, treatment, and long-range prognosis.

Data on Series of 136 Cases

Method and Material.—Since Jan. 1, 1948, 155 patients have been treated for noninvasive carcinoma of the uterine cervix at the United States Naval Hospital, San Diego, California. However, only 136 cases are suitable for analysis because of incomplete records and practically no follow-up in 19 cases.

The 136 patients exhibited all the acceptable criteria for cancer in situ. In brief, these criteria consist of all the microscopic evidence of malignancy minus invasion of the underlying stroma.¹

Age and Race Distribution.—Table I gives the age and race of the 136 patients studied. It will be immediately evident that the age range is from 21 through 58 and the average age is about 34.5 years. This is by far a younger age distribution than that found in a similar number of patients with invasive cancers of the cervix as emphasized by Carter and associates² in a recent publication. Also, it will be noted that the entire group except for 2 patients was

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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of the white race. This may be partially explained by geographical differences in population in our series but is certainly not a true distribution as judged by other reports.²

TABLE I. AGE AND RACE DISTRIBUTION OF ALL PATIENTS IN SERIES

	NO. OF PATIENTS	% OF TOTAL
<i>Age in years.—</i>		
21	2	1.4
22	2	1.4
23	2	1.4
24	1	0.7
25	7	5.1
26	7	5.1
27	8	5.8
28	6	4.4
29	9	6.6
30	11	8.0
31	8	5.8
32	10	7.3
33	7	5.1
34	11	8.0
35	8	5.8
36	5	3.6
37	5	3.6
38	5	3.6
39	1	0.7
40	2	1.4
41	4	2.9
42	3	2.2
43	2	1.4
44	1	0.7
45	4	2.9
46	2	1.4
48	1	0.7
58	2	1.4
Average age	34.5	
Age range	21-58	
<i>Race.—</i>		
Caucasian	134	98.5
Unknown	2	1.5

Diagnosis.—The establishment of the diagnosis of cancer in situ of the uterine cervix is difficult. In the year 1948 the Department of Gynecology participated in a clinical study in close alliance with the Department of Pathology of our hospital in one of the first evaluations of the use of the Papanicolaou smear for general screening of gynecology patients in the San Diego area. A complete account of this work was subsequently published by Sarkisian,³ emphasizing the unquestioned value of such a screening aid. Since that time we have performed a Papanicolaou smear on every new gynecological patient, and the results have been extremely gratifying. Martin and his associates⁴ also reported the results of a more recent five-year screening study in the City of San Diego, verifying the value of the smear as a routine screening procedure for all gynecological patients.

TABLE II. TOTAL NUMBER OF PAPANICOLAOU SMEARS IN ENTIRE SERIES

TOTAL NO. SMEARS	PAPANICOLAOU CLASSIFICATION					NO SMEAR
	1	2	3	4	5	
121	2	0	29	85	5	15

In Table II will be found the number of Papanicolaou smears reported in the present series. In 15 cases no smear was taken or at least was not reported. As will be noted, the majority of smears were in Classes III and IV, and this is as noted by other investigators.³

Punch Biopsy Versus Conization.—In the early years of the study it was policy in our gynecology clinic first to obtain four quadrant cervical biopsies at 12, 3, 6, and 9 o'clock on all patients with suspicious smears, and if no invasive or preinvasive cancer was found then to proceed to the 360 degree cold knife conization biopsy. In Table III it will be noted that 55 multiple biopsies are listed. Also in Table III are listed the number of cone biopsies performed and their distribution in accordance with the microscopic evidence of cancer. There were no cones with microscopic evidence of invasive cancer reported.

TABLE III. COMPARISON OF PATHOLOGY IN PRETREATMENT BIOPSIES AND POSTOPERATIVE SPECIMENS

HISTOPATHOLOGICAL DIAGNOSIS	MULTIPLE BIOPSY		CONE BIOPSY		POSTOPERATIVE SPECIMEN	
	NO.	%	NO.	%	NO.	%
No evidence of cancer in situ	2	3.6	10	7.6	96	72.7
Cancer in situ without gland involvement	41	74.5	75	57.7	22	16.7
Cancer in situ with gland involvement	11	20.0	45	34.7	12	9.1
Invasive cancer	1	1.9	—	—	2	1.5
					36	27.3
Total	55	100.0	130	100.0	132	100.0

Because of the difficulty in establishing a firm diagnosis by multiple biopsy alone and then by subsequent conization in cases where the tissue was traumatized, it was strongly urged by Peterson and Harris⁵ to bypass the multiple biopsy in the clinic in favor of a more generous cone to be obtained in the operating room. This policy is now almost 100 per cent in operation in our clinic at this time. Only obvious cervical lesions are now biopsied in the clinic in the hope of establishing a diagnosis without recourse to hospitalization. As noted in Table III, 130 patients were subjected to conization prior to any therapy being initiated.

Comparison of Microscopic Pathology in Biopsy and Cone.—Further examination of the data disclosed a discrepancy in the microscopic pathology in the multiple biopsy and the conization biopsy subsequently obtained. These data are given in Table IV. It will be evident that 10 biopsies were reported as positive for cancer in situ and when the cervixes were subsequently coned and examined by multiple-block technique they were found to be negative for any evidence of cancer in situ or invasive cancer. This information was recently emphasized by Peterson and Harris.⁵ These same biopsies were evenly divided between involvement and no involvement of glands and from this standpoint may indicate that glandular involvement is no evidence that residual tumor will be found in the subsequent cone or postoperative specimen. It will be noted, however, that in 6 cases there was progression from lack of glandular involvement in the biopsy to definite involvement of endocervical glands in the more inclusive conization biopsy and in no instance was this condition found to be reversed. It should also be noted that 3 postoperative cervixes contained residual tumor even though no cancer was found in the pretreatment conization biopsy. This may indicate that involvement of the glands by tumor

cells is indeed a step further in the direction of actual stromal invasion, as suggested by Galvin and Te Linde⁶; also, a negative cone is no definite assurance that complete removal of the tumor has been accomplished by the multiple biopsy.

TABLE IV. COMPARISON OF MICROSCOPIC PATHOLOGY IN BIOPSY AND CONE SPECIMEN IN SAME PATIENTS

MICROSCOPIC PATHOLOGY	BIOPSY		CONE	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Cancer in situ of cervix	10	2	2	10
Cancer in situ without gland involvement	6	0	1	6
Cancer in situ with gland involvement	4	0	1	4
Positive biopsy without gland involvement to cone with gland involvement				6
Positive biopsy with gland involvement to cone without gland involvement				0

Concurrent Pelvic Pathology.—In the examination of all the eligible patients who make up this series there was noted pathology in the pelvis in some that actually was the prime consideration for therapy prior to the reporting of the positive or suspicious smear that led to further study and final diagnosis of cancer in situ of the cervix. These conditions are listed in Table V in the order of their frequency. It will be noted that no concurrent pelvic pathology was found in 80 instances.

TABLE V. CONCURRENT PELVIC PATHOLOGY IN TOTAL CASES IN SERIES

CONCURRENT PELVIC PATHOLOGY	NO.
None	80
Chronic cervicitis	19
Cervical erosion	11
Chronic pelvic inflammatory disease	8
Cystocele	7
Rectocele	4
Ovarian cyst, benign	4
Fibromyoma of uterus	3
Pregnant uterus	4
Vaginitis, nonspecific	2
Perforated uterus	1
Intraligamentous hematoma	1
Previously irradiated cervix	1
Retroversion of uterus	1
Ovarian carcinoma	1
Adenomyosis of uterus	1
Pelvic endometriosis	1
Leukoplakia of cervix	1
Total	70

Treatment.—Following the establishing of the diagnosis, all cases were subjected to some definitive therapy except 4. Three of the latter were treated by observation only as the cone was found to be negative for cancer following a positive biopsy in each case; the fourth was cone positive but could not be treated further as the patient developed an acute schizophrenia and it was not considered advisable to subject her to additional surgery. Table VI contains the method of management utilized in all cases treated in the series. Seven patients subjected to hysterectomy did not have positive cones and one may question why the operative procedures were carried out. Five of these patients were treated in such a manner because it was extremely difficult to convince

them that they did not require further treatment for a cancer they were convinced they had. The remaining 2 hysterectomies were performed for benign concurrent pelvic pathology.

TABLE VI. METHOD OF MANAGEMENT EMPLOYED IN ALL CASES TREATED IN SERIES

METHOD OF MANAGEMENT	NO CONE	EXTENT OF CONE PATHOLOGY			TOTAL
		NEGATIVE FOR CANCER	CANCER IN SITU WITH- OUT GLAND INVOLVE- MENT	CANCER IN IN SITU WITH GLAND INVOLVE- MENT	
Total hysterectomy plus excision wide vaginal cuff	5	7	71	39	122
Observation alone					
Cone positive cases	—	—	—	1	1
Cone negative cases	—	3	—	—	3
Combined irradiation and surgical therapy	—	—	—	4	4
Resection of cervical stump	1	—	4	1	6
Total	6	10	75	45	136

Therefore a total of 132 cases were treated definitively by surgery alone or in combination with some form of irradiation, and 4 cases were allowed to remain untreated for the reasons listed above.

Comparison of Pathology in Pretreatment Biopsies and Postoperative Specimens.—In Table III are compared the pretreatment multiple biopsies and conization biopsies with the pathology found in the postoperative specimens. In 36 cases, or 27.3 per cent, residual cancer was found in the cervix. Two cases, or 1.5 per cent, were found to be actually invasive cancer. The cone biopsies in each of these latter cases showed extensive in situ involvement of the endocervical glands.

Comparison of Extent of Pathology in Cone and Postoperative Specimen.—To analyze further the cases with residual tumor present in the postoperative cervix from the standpoint of degree of pathology found in the pretreatment cone we note in Table VII that of the 36 cases with residual tumor present there were 33 conization biopsies performed. From these data it appears that the extent of the microscopic pathology in the cone does not necessarily predetermine the presence of residual tumor in the postoperative specimen. Also in retrospect a good all-inclusive conization biopsy is no absolute assurance there will be no residual tumor in the postoperative specimen as evidenced by the 3 cases with residual tumor preceded by a negative cone and the 27.3 per cent residual tumor incidence in our series.

TABLE VII. EXTENT OF PATHOLOGY IN CONE BIOPSY AND RESIDUAL PATHOLOGY IN POSTOPERATIVE SPECIMEN

MICROSCOPIC PATHOLOGY	CONE-BIOPSY	POSTOPERATIVE SPECIMEN
No evidence of cancer in situ	3	0
Cancer in situ without gland involvement	16	22
Cancer in situ with gland involvement	14	12
Invasive carcinoma cervix	0	2
Total	33	36*

*Includes three postoperative uteri not previously coned.

By way of explanation it should also be stated here that 3 of the patients with residual tumor did not have a pretreatment cone biopsy as the hysterectomy was performed primarily for other reasons than removing an in situ

cancer of the cervix. If these cases were deducted from the over-all figure it still leaves 33, or 25 per cent, of the 132 cases with residual tumor in the post-operative specimen.

TABLE VIII. PRESENT CLINICAL STATUS OF ALL PATIENTS IN STUDY

PRESENT CLINICAL STATUS	YEARS POST TREATMENT							TOTAL	
	1	2	3	4	5	6	7	NO.	%
No evidence of recurrence or residual disease when last seen	18	9	17	6	6	5	2	63	46.4
No evidence of disease when last seen but lost to follow-up	32	14	10	9	5	3	0	73	53.6
Combined groups both free from disease when last examined	50	23	27	15	11	8	2	136	100.0

Present Clinical Status of Patients in Study.—Upon referring to Table VIII it will be immediately evident that adequate follow-up has been difficult to maintain over any long period of time. Sixty-three cases have been followed in the Gynecology Tumor Clinic for from one to seven years, the majority for only three years. On the other hand 73 cases, or 53.6 per cent, have been lost to follow-up after from one to seven years, the majority again after three years. To the best of our knowledge these patients were all in good health and free from recurrent or residual disease when last seen. Twenty-one patients of the combined group have been followed for over five years without developing any evidence of recurrent or residual disease. Also, there have been no deaths from cancer in this series to date in the followed cases.

TABLE IX. PRESENT CLINICAL STATUS IN RELATION TO PRETREATMENT CONE PATHOLOGY

MICROSCOPIC PATHOLOGY IN CONE	YEARS POST TREATMENT							TOTAL
	1	2	3	4	5	6	7	
No evidence of cancer	6	4	—	—	—	—	—	10
Cancer in situ of cervix without gland involvement	19	17	17	8	6	8	—	75
Cancer in situ of cervix with gland involvement	16	8	9	8	4	—	—	45
Invasive cancer	—	—	—	—	—	—	—	—
Total	41	29	26	16	10	8	—	130

Clinical Status in Relation to Pretreatment Pathology in Cone.—In Table IX is presented the clinical status of cases in respect to the pretreatment microscopic pathology in the cone. It will be noted that all cone-negative patients are free from disease after one and two years, 6 and 4 cases, respectively. The remainder, with and without involvement of the endocervical glands, appear to have survived equally well for similar periods of time, which tends to make one feel that glandular involvement is not necessarily indicative of a poor prognosis in any individual case.

Comparison of Clinical Status of Patients With and Without Residual Tumor in Postoperative Specimen.—Another method that can be used in determining prognosis is to investigate the cases with residual tumor in the post-operative specimen and those without residual from the standpoint of salvage after five years. These data, contained in Table X, disclose that 16.6 per cent of the patients with residual tumor have survived for five years or more, while 15.6 per cent of those without residual tumor have also survived for the same period. Thus it appears from these data that the mere presence of residual tumor in the specimen is no definite evidence in favor of a poor prognosis in any individual case.

TABLE X. PRESENT CLINICAL STATUS OF PATIENTS WITH RESIDUAL TUMOR IN SPECIMEN COMPARED WITH PATIENTS WITHOUT RESIDUAL TUMOR IN SPECIMEN

	YEARS POST TREATMENT							TOTAL	
	1	2	3	4	5	6	7	NO.	%
<i>Patients With Residual Tumor.—</i>									
Alive and well last examination	2	5	8	2	1	2	2	22	
Lost to follow-up	7	2	3	1	—	1	—	14	
Combined group total	9	7	11	3	1	3	2	36	27.3
<i>Patients With No Residual Tumor.—</i>									
Alive and well last examination	15	4	9	4	5	3	—	40	
Lost to follow-up	23	11	7	8	5	2	—	56	
Combined group total	38	15	16	12	10	5	—	96	72.7
Total cases treated by observation only								4	2.9

Cancer in Situ of Cervix and Pregnancy.—Table XI contains a summary of each case that was associated with pregnancy. It will be noted that early in the study it was policy to carry out treatment of each case immediately after the termination of the pregnancy without doing re-evaluation studies. At the present time it is policy to re-evaluate every case that is diagnosed by cone during pregnancy and if the cone is found to be negative at six weeks after delivery the patients will be followed by periodic Papanicolaou smears until such time as rebiopsy or conization seems to be indicated. We feel, as do others,² that pregnancy sometimes produces changes in the cervical epithelium that appear to be microscopically malignant but apparently have the ability to revert to normal after the pregnancy has terminated. Of the 4 cases in our series, 3 were actively treated and one has been observed with smears only for a period of one year without recurrence or residual disease becoming manifest.

TABLE XI. PREGNANCY AND CANCER IN SITU OF CERVIX IN TOTAL PATIENTS IN SERIES

1. Cone biopsy disclosed cancer in situ without glandular involvement during early pregnancy and patient aborted. Total abdominal hysterectomy done and no residual tumor found in uterus. Alive and well six years later.
2. Cone biopsy during pregnancy showed cancer in situ with glandular involvement. Total hysterectomy with wide vaginal cuff excision and pelvic lymphadenectomy done after delivery of infant at term. No residual tumor in uterus. Lost to follow-up after one year.
3. Cone biopsy during pregnancy showed cancer in situ without glandular involvement. Total hysterectomy with wide vaginal cuff excision and left salpingo-oophorectomy after delivery of term baby. No residual tumor in uterus. Alive and well two years later.
4. Cone biopsy during pregnancy revealed cancer in situ with glandular involvement. Patient delivered a term infant. Reconization biopsy after delivery negative for cancer. Treated by observation only. Alive and well one year later.

One of our nonpregnant patients was treated previously with irradiation for cancer of the cervical stump in 1948. In August of 1955, a conization biopsy following a suspicious smear report was diagnosed as cancer in situ. There was no involvement of the cervical glands. The cervical stump was resected vaginally without incident and the specimen did not contain residual tumor. The patient has been followed for the past six months without evidence of recurrence or residual disease. This type of case makes one wonder whether this represents a new tumor or a residual of noninvasive cancer lying dormant all of these years.

Comment

The diagnosis of carcinoma in situ of the uterine cervix and its treatment have occupied the attention of many investigators for several years.^{2, 6, 7} It is

quite universally accepted that evidence of stromal invasion and not involvement of the endocervical glands is the necessary criterion to look for when excluding the presence of invasive cancer in any microscopic section.⁷ Several years ago Foote and Stewart⁷ successfully demonstrated that carcinoma of the cervix in its noninvasive form was not grossly evident to the naked eye and required microscopic investigation of considerable tissue before a true diagnosis could be determined in any case. They favored the four-quadrant-biopsy technique and reported considerable success with its use in all cases. It also was emphasized, however, that *in situ* cancer could not be diagnosed without completely eliminating the possibility of stromal invasion and to do this it was mandatory to perform a 360 degree cold knife cone biopsy in each case. The tissue would then be cut into many sections and a search made for evidence of stromal invasion. This procedure has been followed in the U. S. Naval Hospital, San Diego, California, for the past seven and one-half years and our positive cone cases have all been processed in the manner just described.

The treatment of cancer *in situ* of the cervix in our hands has been as described in a previous publication¹ and as recommended by most major clinics in this country.^{2, 7} We elect to do a total abdominal hysterectomy with resection of a generous portion of the vaginal cuff in each case and do not remove the ovaries unless they are diseased or the patient is over the age of 45. We do not prefer the vaginal route as do certain investigators² as it is felt that the abdominal route has the advantage of better exposure for surgery of the adnexa and that vaginal hysterectomy is attended by more trauma to the cervix. Such manipulation is best avoided when surgery is performed for a malignant condition.

An analysis of our present series of 136 cases is by no means large enough to be of any statistical significance but does provide substantiating evidence for continuing our present method of management.

From the results of this study and the previous investigations carried out by Peterson and Harris⁵ in our institution and by Martin and associates⁴ in the City of San Diego, the value of the Papanicolaou smear as a screening tool is now definitely established and it is evident that no gynecological or obstetrical service can operate efficiently without this diagnostic aid.

The majority of the cone specimens did not show involvement of the endocervical glands. It is to be noted, however, in Table III, that of 45 cases with glandular involvement in the cone specimen, 14, or 31.1 per cent, showed residual tumor in the postoperative specimen, including 2 invasive cancers, as opposed to 22, or 29.3 per cent, of 75 cone specimens without glandular involvement that showed residual tumor. This relatively high incidence of residual tumor in the cases with glandular involvement in the cones suggest that such involvement represents a more advanced stage of cancer *in situ*. These data of course are not acceptable as evidence for actual invasion of the stroma as suggested by others,⁶ but merely indicates incomplete removal of the tumor by extensive conization or possibly a multicentric origin of cancer *in situ*.

In certain smear-suspicious cases where we are confronted with the problem of treatment when the biopsy is reported positive and the subsequent cone is found to be negative, we feel there are certain extenuating circumstances which must be weighed carefully in each case before deciding upon definitive therapy. These are the age of the patient, her desires concerning childbearing, presence of other pelvic pathology, and pregnancy. Any of these could be a reason for conservatism and periodic follow-up by smear. There are 3 patients in our series now under such management; 2 have been free from recurrence or residual for one year and the remaining patient was followed for two years before being lost to follow-up.

Statistical Data on 6 Cases in Study Treated Surgically Before Performance of Diagnostic Conizations

An analysis of the 6 cases in our series in which conization was not done prior to operation was found to be highly revealing. The pertinent data in each case are found in Table XII. Certainly, after a study of these cases it is quite evident that the Papanicolaou smear must be used in all instances prior to contemplated pelvic surgery and that multiple biopsy is highly inadequate when compared to the full 360 degree cold knife conization biopsy.

TABLE XII. STATISTICAL DATA ON 6 CASES IN SERIES WITHOUT CONIZATION BIOPSY BEFORE OPERATION

STATISTICAL DATA	WITHOUT CONIZATION BIOPSY					
	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6
1. Papanicolaou smear data	0	—	3-4	0	0	3-4
2. Multiple biopsy performed	No	No	Yes	Yes	Yes	Yes
3. Conization biopsy performed	No	No	No	No	No	No
4. Biopsy pathology	0	0	Invasive	Cancer in situ	Cancer in situ	Cancer in situ
5. Conization pathology	0	0	0	0	0	0
6. Concurrent pelvic pathology	Yes	Yes	No	No	No	No
7. Type of treatment						
a. Total hysterectomy	x	x	x		x	x
b. Therapeutic conization						
c. Observation alone						
d. Surgery and irradiation						
e. Resection of cervical stump				x		
8. Pathology in postoperative uterus or cervical stump						
a. No evidence of cancer				x	x	x
b. Cancer in situ without gland involvement	x	x	x			
c. Cancer in situ with gland involvement						
d. Invasive cancer						
9. Present clinical status						
a. Alive and well		5 years	7 years	5 years		6 years
b. Lost to follow-up	1 year				2 years	

The follow-up on all of our cases has proved to be quite a problem. All of our patients are wives of servicemen some of whom have been discharged to civilian life and they have been lost to follow-up as a result of not sending their last address to the Tumor Board Secretary. We record them to be alive and well as of their last visit.

The five-year survival figures in our series are of no statistical significance but they do enable us to postulate a possible trend in the bearing that glandular involvement may have on five-year salvage. Table IX demonstrates that 14 cases out of 75 were without glandular involvement, or about 18.6 per cent have been free from disease for over five years. Four patients out of 45 with glandular involvement, or 8.8 per cent, have attained the five-year survival level. While no deaths have occurred in this series nor has recurrence of the disease been noted, the arbitrary selection of five-year survival as a basis for judgment questions the ultimate prognosis when glandular involvement is present in the original pathology.

Concerning cases of cancer in situ of the cervix that have been diagnosed by cone during the pregnant state it is thought best at the present time to allow these patients to proceed to term and to be delivered via the vaginal route unless some obstetrical reason is present to alter such a plan. After delivery the patient is again evaluated by re-conization at six to eight weeks post

partum and if the microscopic evidence of cancer in situ is found then definitive therapy can be carried out. This policy is endorsed by most major clinics in this country to the best of our knowledge at the time of this writing.

Summary

One hundred thirty-six cases of carcinoma in situ of the uterine cervix have been analyzed to determine the possible prognostic significance of endocervical glandular involvement in in situ tumor in the pretreatment conization biopsies.

One hundred thirty conization biopsies were performed prior to initiation of any definitive therapy. Forty-five cases, or 34.7 per cent, were found to have involvement of the endocervical glands; 10, or 7.6 per cent, were negative for cancer; and the remainder were positive for cancer in situ without glandular involvement.

Thirty-six, or 27.3 per cent of the 132 patients treated, were found to harbor residual tumor in the postoperative specimens. Fourteen, or 38.8 per cent of the cases with residual tumor in the postoperative specimen, were derived from the 45 conization biopsies with endocervical glandular involvement, for an incidence of 31.1 per cent. The remaining 22 cases, or 61.2 per cent, were derived from 75 conization biopsies without involvement of the endocervical glands, for an incidence of 29.3 per cent.

Sixty-three patients, or 46.4 per cent of the total series, have been adequately followed since being treated and 73, or 53.6 per cent, have been lost to follow-up over a period of seven years. Twenty-one patients, or 15.4 per cent of the combined groups, have been free of recurrence over five years.

Fourteen, or 18.8 per cent of the seventy-five patients without involvement of the endocervical glands in the conization biopsies, have been followed for five years without recurrence of disease, whereas 4, or 8.8 per cent of the 45 with glandular involvement in the conization biopsies, have attained the five-year salvage mark safely.

Fifteen, or 15.6 per cent of the 96 patients without residual tumor in the postoperative specimens, were followed for five years without recurrence of disease, while 6, or 16.6 per cent of the 36 with residual disease in the postoperative specimens, were also followed uneventfully for a five-year period.

Six patients in the series had extensive glandular involvement in the conization biopsies and no involvement of glands in the preceding quadrant biopsies, thus demonstrating a progression of the disease microscopically.

Both cases of invasive cancer of the cervix diagnosed in the postoperative specimens in the series were preceded by extensive endocervical glandular involvement in the cones.

There were 3 cases of residual tumor in the postoperative specimen that were preceded by conizations negative for evidence of cancer.

There were 4 cases in the series that were diagnosed during pregnancy and treatment was individualized in each case as noted in Table XI.

There have been no deaths in the series to date that could be attributed to carcinoma in situ of the uterine cervix to the best of our knowledge.

Conclusions

From the results of this study the following conclusions may be drawn:

1. The Papanicolaou smear for the investigation of cervical malignancy is an invaluable screening aid and should be obtained on each patient prior to the initiation of any elective pelvic surgery.

2. The diagnosis of cancer in situ is possible only if the 360 degree cold knife conization biopsy technique is carried out in every case of suspected cervical malignancy.

3. Total hysterectomy and resection of a generous vaginal cuff with preservation of normal-appearing ovaries in all women under the age of 45 is the treatment of choice in all conization-positive cases of carcinoma in situ of the uterine cervix. Any other form of therapy except in certain conditions noted below is considered inadequate as evidenced by the high incidence of residual tumors noted in our series.

4. The presence of glandular involvement in the conization biopsies in our series did not appear to affect adversely the prognosis over a five-year period nor to increase materially the incidence of residual tumor in the post-operative specimen.

5. Extensive glandular involvement by noninvasive cancer in the conization biopsy is considered to be a more advanced stage of the disease from the standpoint of microscopic pathology but it does not constitute invasion of the underlying stroma nor adversely affect long-range prognosis in any case.

6. The incidence of residual tumor in our series is thought to be due to incomplete removal of the tumor by conization biopsy, to its possible multicentric origin, or to a combination of both, and not to involvement of the endocervical glands.

7. Observation with periodic smears in all biopsy-positive cone-negative cases appears to be justified in younger women in the childbearing age and during pregnancy as long as the patient understands fully and accepts the calculated risk involved.

8. A negative conization biopsy does not completely assure total removal of the tumor from the cervix as noted in 3 cases studied in our series.

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CARCINOMA OF THE VULVA*

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THE steady increase in life expectancy has placed vulvar cancer in a more prominent position in the field of female pelvic malignancies. Statistically, the increase in cancer of the vulva is manifested in the cases collected for this presentation. These were compiled from the records of the Mercy Hospital Institute of Radiation Therapy and Clinics, and Lewis Memorial Maternity Hospital. From 1939 through 1955 (a 17 year survey) the total number of cases seen was 41. Of this group 43.9 per cent have been seen in the last 5 years. A similar increase has been noted in other reported series.⁴

Since this disease is now being encountered more frequently, it is important that we have a thorough understanding of it and a definitive plan of therapy. Cases treated prior to 1940 had a poor 5 year salvage. Lunin⁸ reported an 18.1 per cent survival in his series, others^{5, 6, 9} reported series treated prior to 1940 with similar experiences. The reason was, obviously, the haphazard method of therapy. Irradiation therapy, local excision, hemivulvectomy, etc., were some of the methods employed. The end results proved the inadequacy of treatment.

Causative Factors and Symptomatology.—Carcinoma of the vulva develops slowly. In most cases the list of symptoms suggests its onset years prior to gross or microscopic evidence of the disease. We may assume this to be the gestational period of vulvar cancer. Chronic irritation from scratching is probably a factor. Collins² has shown that other chronic irritative conditions are probably primeval, since 66 per cent of Negro patients in his series under 50 years of age had some granulomatous venereal disease in conjunction with vulvar cancer. Whether this is a primary reagent or merely a catalyst is not known. Leukoplakia is also frequently seen with malignant lesions, yet this finding is, many times, present years prior to the development of malignant neoplasms. It is logical to believe the transformation is a gradual one. This is the view held by most authorities in the field.

Other symptoms in more or less the order of their frequency are: swellings with or without bleeding, pain, dyspareunia, dysuria, incontinence, and a mass in the groin with or without suppuration. The latter three are the late symptoms, the incontinence due to urethral destruction and the groin symptoms due to lymphatic spread.

Incidence.—Of all cervical, endometrial, and vulvar carcinoma in our department, the incidence of vulvar carcinoma is one in 49 cases. Parity and marital status do not seem to be factors. Vulvar lesions are found bilaterally in about 10 per cent of the cases⁵ reviewed. In about half the cases, there are palpable lymph nodes. Since lymphadenopathy may be due to infection

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and metastasis only microscopic, the presence or absence of lymphatic gland enlargement is not of great significance. Cosbie⁴ stated, "Massive confluence with fixation is the only absolute clinical manifestation of malignancy."

Diagnosis.—The diagnosis of vulvar malignancy must include the search for precancerous and in situ lesions as well as the obviously malignant cases. A thorough gynecologic examination will include a careful inspection of the vulva. Any ulceration, lump, pigmentation, or deviation from the normal appearance of the skin requires further investigation. The Negro patient has a high incidence of granulomatous venereal disease and a diagnostic survey of all ulcerative lesions should include serologic and dark-field studies for the presence of *Treponema pallidum*, smears for the Duerrey bacillus and Donovan bodies, and a Frei test for lymphogranuloma inguinale. Multiple biopsies are also necessary to diagnose malignancy, tuberculosis, or any of the mycotic diseases. One must remember that granulomatous diseases and malignancy may coexist. Fortunately, such combinations of neoplasms and inflammation have a better prognosis. The inflammatory reaction produced by the granuloma causes regional adenitis which effectively blocks the lymph channels and glands barricading the natural pathways for vulvar malignancy to metastasize.

Any lesion of the vulva producing chronic irritation which does not respond to medical management must be biopsied. We agree with Collins³ that if the biopsy reports are negative and the lesions persist, the entire vulva should be excised and submitted for multiple section study. This is especially important when we remember that vulvar cancer may arise from multiple foci. Pigmented lesions should also be removed with a wide margin of adjacent tissue since malignant melanomas also occur in this region.

Therapy

Vulvar malignancies are of a mature cell type and are relatively radio-resistant. Further, the vulvar tissues are easily injured by irradiation and the resulting ulceration and edema are exceedingly painful. Irradiation, then, though occasionally used for palliation, has no place in the primary management of vulvar cancer.

Definitive treatment of carcinoma of the vulva is nothing less than radical surgical excision. Such planned therapy during the past fifteen years has resulted in salvage rates approaching 60 per cent. The extent and method of approach, however, require careful individualization. Since it is a disease of older women, other serious organic disease may accompany vulvar malignancy. Advances in recent years in assisting the patient during operation with whole blood and improved anesthesia plus meticulous postoperative management with antibiotics and electrolyte and fluid balance have made it possible to rescue many patients from the ranks of the inoperable.

The ideal approach is the one-step radical node dissection and vulvectomy as advocated by Stanley Way.¹¹ His operative mortality of 12 per cent, however, with salvage rates no better than those obtained by more individualized plans of therapy, casts doubt on this as a universal approach to the problem. So, too, the more radical surgery for the far-advanced cases with bowel and/or bladder involvement, as advocated by Brunschwig,¹ resulted in an operative mortality of 45 per cent. Such figures must be lowered before such extensive exenteration procedures are practicable.

Our plan of therapy has been one of individualization. The absolute contraindications for surgery are lung or long bone metastases. Chest plates and skeletal x-ray studies are an essential part of the preoperative preparation of the patient. In relatively young women, who are good operative risks, the

Way operation is performed. In many instances, however, the constitutional reserve of the patient will not withstand such a prolonged one-stage operation. In such patients, a very adequate radical vulvectomy is of prime importance. When the primary lesion is located nearer the posterior portion of the vulva, then a thorough dissection of the ischiorectal fossae is necessary. McKelvey⁷ pointed out that he has seen only one patient who died of or with tumor after radical vulvectomy who did not have local vulvar recurrence. He emphasizes that "there is no use removing iliac glands until control of the local tumor is achieved."

If the poorer risk patients are able to withstand the original vulvectomy then node dissection may be carried out when the patient has adjusted to the initial surgical assault. The gland dissection must, of course, be bilateral since the lymphatic pathways decussate from one side to the other. The extent of the node dissection should depend on the physical condition of the patient and the pathology encountered. The superficial and deep inguinal nodes, femoral nodes, and the node of Cloquet should always be excised. If glands are encountered which are questionably involved then further surgery is justified. It is possible for such doubtful nodes to be incised, smeared, stained, and examined for any malignant cells at the time of operation. Positive nodes in the inguinal area certainly demand dissection of the external iliac, obturator, and hypogastric nodes. If the patient is a poor risk this may be a third-stage procedure.

If adequate surgery is carried out, primary closure is not always possible. The postoperative care, therefore, must be prolonged and painstaking. Frequent débridement of the vulvar area and groin is often necessary. Skin grafting in such denuded areas is rarely successful and better results are usually obtained by allowing epithelization to take place from the margins of the wound. Sometimes as long as three or four months are required before the raw surfaces are completely epithelized. Such an inconvenience is necessary if local recurrences are to be prevented.

Material and End Results

An analysis of our cases will help to demonstrate the value of planned therapy and also will serve to reveal the inadequate salvage rates with local excision and irradiation.

All cases registered in our department as carcinoma of the vulva during the years 1937 through 1955 number 41. However, 18 patients have made their initial visits within the past 5 years and only 23 were seen initially prior to that time. These include 5 who received palliative x-ray in our department and 4 who were operated upon elsewhere. As shown in Table I, 6 patients have survived 5 years or more. One patient has been lost to follow-up, though living and well 4 years postoperatively. Two patients lost to follow-up had recurrences within 5 years and no follow-up was obtainable on 4 other patients. If we consider all 7 patients lost to follow-up as not having survived, the overall 5 year survival rate is 26 per cent.

Of the 16 patients we were able to follow through the arbitrary period of 5 years or more, the longest survival was 14 years. Table II includes these patients only and the corrected 5 year survival rate is 37.5 per cent.

Three of these patients were treated by radical vulvectomy and external irradiation and 3 by radical vulvectomy and bilateral inguinal and femoral node dissection. In none of these patients were there palpable lymph nodes and in none of the lymph nodes removed was carcinoma found. One patient who has survived 6 years was treated with intracavitary radium two years ago for carcinoma of the endometrium. Her general condition precludes further major surgery.

TABLE I. SURVIVAL FIVE YEARS OR MORE

<i>Follow-up 5 Years or More.—</i>	
Living and well, 5 years or more	6
Died with disease, less than 5 years	5
Died, cause unknown, in less than 5 years	5
<i>Lost to Follow-up in Less Than 5 Years.—</i>	
Living and well (4 years)	1
Living with disease	2
Lost to follow-up	4
Total	23
5 year survival rate	26%

TABLE II. PATIENTS FOLLOWED FIVE YEARS OR MORE

Living and well, 5 years or more	6
Died with disease in less than 5 years	5
Died, cause unknown, in less than 5 years	5
Total	16
5 year survival rate	37.5%

Certainly the corrected 5 year survival of 37.5 per cent is not an acceptable figure today. Such results were due to the inadequate therapy employed in some of the earlier cases. No patient who had less than a radical vulvectomy has survived beyond 4 years. If we review the results of just those patients who were adequately treated, however, our survival figures approach an acceptable percentage. Of the 23 cases under study, there were 11 who had radical vulvectomies performed and 7 of these also underwent bilateral inguinal and femoral lymphadenectomy. In only 1 of these was cancer found in the lymph nodes. She lived less than one year. Of the 4 patients treated by radical vulvectomy and external radiation, 3 survived. Of the 11 patients treated by radical vulvectomy with or without lymphadenectomy, 6 survived (Table III). The survival in this adequately treated group is 54.5 per cent. This compares favorably with Taussig's¹⁰ report of 58.5 per cent survival of patients treated by radical vulvectomy and Basset's operation. His over-all 5 year survival in 155 cases was 32 per cent. Diehl⁵ reported a 54.5 per cent 5 year survival rate in 11 cases treated by this method.

TABLE III. SURVIVAL IN CASES TREATED BY RADICAL VULVECTOMY

TREATMENT	NUMBER OF PATIENTS	5 YEAR SURVIVALS
Radical vulvectomy and radiation	4	3
Radical vulvectomy and lymphadenectomy	7	3
Total	11	6
5 year survival rate		54.5%

Table IV is a summary of treatment employed and the results obtained in all 23 cases. Of the 5 patients treated by palliative radiation alone, one refused operation and one allowed only two treatments to be given. Of those treated by local excision and radiation, one was alive with disease after 4 years and another alive and well after 4 years. These were both lost to follow-up in less than 5 years.

A further breakdown of the 7 cases treated with less than radical vulvectomy shows that one patient did not return for contemplated extensive removal and one was 92 years of age and her remaining years were not only made more comfortable, but no doubt extended by the omission of a radical

procedure. Two of these were referred to our department after operation had been performed. The remaining 3 patients were treated in the early 1940's and serve to remind us that preoperative irradiation followed by local excision was, at that time, an accepted form of treatment of cancer of the vulva.

TABLE IV. SUMMARY OF TREATMENT

	NUMBER OF PATIENTS TREATED	5 YEAR SURVIVALS
Radical vulvectomy with radiation	4	3
Radical vulvectomy with lymphadenectomy	7	3
Palliative radiation alone	5	0
Simple vulvectomy or local excision with radiation	7	0
Total	23	6

TABLE V. CASES SEEN SINCE 1950

TYPE OF TREATMENT	NO. OF PATIENTS
Simple vulvectomy	1
Radical vulvectomy	4
Inguinal lymphadenectomy	1
Radical vulvectomy and inguinal lymphadenectomy	12
Total	18

Eighteen additional patients have registered in the department in the past 5 years, 7 of these within the past 12 months. The treatment of these is listed in Table V. The case treated by simple vulvectomy was diagnosed as intraepithelial carcinoma. Of the 4 patients treated by radical vulvectomy, one refused further operation and another had a diagnosis of hidradenoma of the vulva. Inguinal lymphadenectomy was performed in one woman as a first-stage procedure. She experienced a blood transfusion reaction, however, and died 7 days postoperatively of lower nephron nephrosis. These nodes showed metastasis. Of the remaining 12 patients treated by radical vulvectomy and Basset operation, 5 have already died with the disease; 3 of these had cancer in the lymph nodes. None of the remaining 7 patients so treated had positive nodes. Table VI summarizes the incidence of positive nodes. Of the total 5 patients with proved spread to the inguinal lymph nodes in the entire series, none has survived beyond 2½ years.

TABLE VI. INCIDENCE OF PROVED LYMPH NODE METASTASES

	1937-1950	1950-1955	TOTAL
Number of lymphadenectomies performed	7	13	20
Number of positive nodes	1	4	5
Positive nodes over-all			25%

External irradiation has been used in several of these recent cases as a palliative procedure. Since this was employed, not as a primary method of treatment, but as a form of alleviating symptoms in the later stages of the disease, the results were satisfactory though by no means astounding.

Since these 18 cases were first seen within the past 5 years, survival statistics are not possible at this time. Additional analysis of our series also shows a rather abrupt change in therapy since 1946. Prior to that time treatment

was not uniform. However, during the past 10 years the policy of the department has been to include in the plan of treatment in each case, radical vulvectomy, removal of the superficial and deep inguinal nodes, the femoral nodes, node of Cloquet, and nodes about the iliac vessels if palpable at the time of operation. Although this has been the original intention, we have not been rigid but have bent our purpose to suit the needs of the patient. Of the 26 patients who were treated during the past ten years, this was carried out in 17 instances; the remaining 9 patients either refused the procedure, were too poor risks, or were found to have less than invasive carcinoma.

Summary and Conclusions

Carcinoma of the vulva is a disease of older women. With the over-all increase in life expectancy there has been a concomitant rise in the incidence of vulvar malignancy, 43.9 per cent of our cases having been seen during the last 5 years. A critical survey of the symptomatology clearly indicates that it is a disease of slow development and that chronic irritative lesions of the vulva are predisposing factors. Such precancerous lesions must therefore be excised. Cases of coexistent carcinoma and venereal granulomas generally have a better prognosis since the accompanying inflammatory adenitis blocks the lymphatic pathways, preventing metastases. When vulvectomy is done for precancerous lesions, the specimen must be cut for multiple section study as previously undetected malignancy may be found. If discovered, then bilateral groin dissection is essential.

Radical surgery is the only means of increasing the 5 year cure rate. The extent of the surgery will depend on the condition of the patient and the extent of the disease. A one-stage procedure is ideal but the reported 12 per cent operative mortality suggests two- or, even, three-stage operations may be best in poor-risk patients. The exenteration operation is not yet practical since the mortality rates are alarmingly high.

Our results parallel those reported by other clinics. The over-all salvage was 26 per cent but in the last 10 years the plan of therapy has been more definite and the patients so treated survived in 54.5 per cent of cases.

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Discussion

DR. CONRAD G. COLLINS, New Orleans, La.—Lunin in 1946 presented a survey of cases of carcinoma of the vulva observed in Charity Hospital in the previous 10 years. Eighteen per cent 5 year cures were recorded. We decided at that time to do a team study

of all cases of malignancy of the vulva admitted to the Tulane Unit. The original team consisted of myself, Drs. Edward Nelson and Jason Collins. We decided to follow a very rigid protocol and though all of the cases on the Tulane Unit were not operated upon by the members of the team, they supervised, prescribed for and carried on the follow-up in all of these cases. All of our residents have done some of these procedures. The tenets which we put down are as follows:

1. If an ulcer was found we wanted to make sure we were dealing with carcinoma before we performed any operative procedure of any sort and the very rigid diagnostic survey described by Dr. Isaacs tonight was followed in detail.

2. We decided that if biopsy showed an intraepithelial carcinoma then an extensive vulvectomy would be performed and the whole vulva submitted to the pathologist for multiple sections. If multiple sections showed no invasion, then we considered vulvectomy sufficient to cure the disease. If, however, invasion was found, then extensive node dissection consisting of removal of the lower aortic, vena cava, external iliac, common iliac, hypergastric, obturator, Cloquet, superficial and deep inguinal and femoral nodes would be carried out. Also the nodes from each of these areas would be put in separate bottles in order that if metastases were found we could plot where metastasis had occurred. In this way the number of metastases occurring in the different regions in the cases that we took care of would be accurately recorded. The important fact deciding whether or not node dissection would be necessary was not whether we were dealing with Bowen's disease, basal-cell epithelioma, sarcoma, adenocarcinoma, or squamous-cell carcinoma, but whether or not the lesion was intraepithelial or invasive as determined by multiple sections. And we cannot too strongly emphasize that in our Clinic therapy is predicated on that point. Also it was decided that, if the lesion were invasive, and had involved other structures such as urethra, bladder, or rectum, in addition to vulvectomy and node dissection wide excision would be practiced plus removal of whatever organs were deemed necessary. Therefore this series contains cases where extensive vulvectomy was performed for intraepithelial carcinoma, to total exenteration and node dissection for extensive carcinoma involving hollow viscera. Also we wish to emphasize that in our Clinic there is no difference in the extent of the vulvectomy which we do for benign or malignant disease with the exception that in malignant disease we clean out both ischiorectal fossae.

Five years ago before this organization we presented a preliminary survey based on only 28 cases. Today, we can give you our results in 54 consecutive cases managed by our team heretofore described. Also, to reiterate, this series is not broken down into whether we are dealing with melanoma, carcinoma, sarcoma, epidermoid carcinoma, or adenocarcinoma. It is a series of all cases of malignancy involving the vulva seen by us since 1946. It was also decided that the age or physical condition of the patient would be no detriment to her having the advantages of surgical therapy. Our youngest patient was 27 and the oldest 87. Approximately half of our patients were under 50 and half were over 50 years of age. The only contraindication to treatment of this disease on our service is metastasis to bone or lung. We would like to state also that we have 100 per cent follow-up and that each case has been followed up as to Jan. 1, 1955. We also wish to emphasize that irradiation in any form was not used in the treatment of malignancies involving the vulva on our service since 1946. The attack is purely surgical, the extent of surgery depending, as we have said before, upon whether or not the lesion was invasive and the local extent. Of the 54 patients seen by us, 3 refused operation. They were all dead within 18 months of the time we saw them. Three were not operated on because of metastasis to lung or bone. All 3 were dead within 4 months. In one case operation was attempted but not completed because of metastasis to soft tissue in the abdomen, namely, liver, bowel, etc. Of the 47 patients operated upon, 10 had vulvectomies only for intraepithelial carcinoma. Only one patient in this group has died and that patient died 10 days postoperatively from a mural thrombus from the heart. A number of these are alive and well and without recurrence 5 years after the extensive vulvectomy. Node dissection was not considered necessary in our cases of intraepithelial carcinoma and our follow-up results seemed to bear out this contention.

Twenty-eight patients had vulvectomy and node dissection for invasive carcinoma and 9 had vulvectomy, node dissection, plus other procedures because of the extent of the disease. Of 28 cases seen between Jan. 1, 1946, and Jan. 1, 1951, allowing for 5 year follow-up, 17 patients are alive and well, a 5 year survival of 61 per cent. We could pad these results if we wished, by eliminating the patients who failed to agree to have operation performed or who were not operated upon because of distant metastasis to lung or bone and this would give us a survival rate of about 74 per cent. However, we believe in dealing with consecutive cases and therefore will put down our 5 year survival in these 28 consecutive cases as being 61 per cent. Of the cases seen between Jan. 1, 1946, and Jan. 1, 1955, which are not eligible for 5 year survival we do have a survival of 60 per cent, which is roughly the same as in the preceding years. Thus by following these precepts and tenets that we set down in 1946 we have increased the survival rate on the Tulane Unit at Charity Hospital from 18 per cent in the decade between 1936 and 1946 to 60 per cent in the decade between 1946 and 1956. Now let us compare these results with those of the other services at Charity Hospital where such a definite regimen was not utilized. From 1946 to 1950 there were 12 cases of malignancy of the vulva observed on the Louisiana State University Service and their survival was 17 per cent. On the Independent Service there were 5 cases admitted. The latter more closely follows the Tulane Unit in therapy than the other unit. Their survival was 60 per cent. Therefore we believe we have good controls as, here in the same hospital with the same type of cases being admitted to all units, the Tulane Unit, following very rigid diagnostic criteria and a very definitely prescribed surgical attack, achieved a 5 year survival of 61 per cent as contrasted with that of other services where neither the diagnostic criteria nor the therapeutic application of surgery is as rigid or extensive as on our service. This is in no way given as a criticism but purely as a statement of fact, giving us, I think, a very definite idea as to what might be the best therapy for carcinoma of the vulva at the present time. In the 37 cases in our series with node dissections, positive nodes were found in 11 cases. Three patients are alive without recurrence, 8 are dead. Two of those who are alive without recurrence, however, have survived a 5 year period. We certainly think it shows that we can accomplish something by node dissection. Of interest is the fact that of the 54 cases observed on the Tulane Unit, 8 had associated primary malignancy of other organs, an incidence of 14.8 per cent, which is very high. This means that if one sees a case of malignancy of the vulva, there is a 1 in 6 chance that primary malignancy of another organ will be discovered at that time or a little later during the patient's life. Of course malignant melanoma is a very serious condition and we have not had any patients with it survive a period of 5 years. We do not do the Stanley Way operation. We do not think this is a good plan for we do not think that metastases occur from one group to another separately and in an orderly procedure but that cancer cells can involve the obturator node without involving any other nodes or the common iliac without involving the superficial or deep inguinal. Therefore if node dissections are to be done, the superficial as well as the deep nodes should be excised. I do not know about the figures quoted in Dr. Isaacs' article regarding Dr. Brunschwig's exenteration for carcinoma of the vulva. I hope that this figure is not true, but whether or not it is, we think that if exenteration is indicated, go ahead and do it. These people are going to die a terrible death if the carcinoma is not removed anyhow. We certainly think that the figure quoted in Dr. Isaacs' paper is much too high. Now a bit about philosophy—if we are going to think like early American Indians and some of the primitive tribes in the world today, removal of a breast or a vulva is a terrible, mutilating procedure. We see nothing mutilating about a vulvectomy for a vulvectomy done for benign or malignant disease, depending upon the extent of the malignancy, can result in a functional vagina. And we believe that, in benign diseases of the vulva which fail to respond to a medical regimen and are still symptomatic with a lot of itching and scratching, the vulva should be removed and that this excision should be wide. Let us not think like primitive tribes, let us think in terms of twentieth-century surgery.

DR. H. CLOSE HESSELTINE.—It should be obvious that the final answer to carcinoma of the vulva is not surgery as such but, until we have a better treatment, surgery

must remain as the principal treatment. In our institution carcinoma of the vulva is in fourth place of the genital malignancies, after cervical, corporal, and ovarian carcinoma. The rate incidence is 3.9 per cent of all female genital malignancies. We concur in the idea that the so-called precancerous lesions of the vulva, or those associated with malignancy, should be removed or appropriately treated. We criticize the use of radiation (x-ray, radium, or other primary sources) for treatment of vulvar malignancies and most other vulvar diseases. Condyloma acuminatum is about the only vulvar disease for which radium or x-ray is used and the dosage is very small.

A few years back my service discontinued the two-stage operations for vulvar cancer and began using the one-stage procedure. This method includes wide resection of the entire vulvar area extending in directions indicated. Then an incision is made on both sides from the lateral areas of the mons veneris upward and laterally but medial to the femoral gland. One may retract the skin to dissect out the inguinal and femoral areas, and enter the abdominal cavity as far as there is indication.

We approach this by placing the patient in a semilithotomy position with the legs slightly abducted, the thighs only slightly flexed on the body, and the legs only slightly flexed at the thighs. This makes it possible for the operator to have full exposure from below while the assistants stand on the outside. Redraping is unnecessary. The table can be tilted or raised as necessary. We employ continuous spinal anesthesia. Usually preparations for replacement of blood loss by fluids and blood are anticipated. The abdominal wall incision extends up almost to the anterior superior spine. This allows retraction and dissection. The entire abdominal flap is freed from the fascia all the way to the umbilicus.

Excess fat is removed but an adequate blood supply is maintained. For closure, a perpendicular incision is made, usually of 5 cm. on the medial side at the upper angle, which allows the flap of the abdominal wall to come down to cover the entire defect anteriorly to the vaginal and urethral area. A few stitches placed under this area to the fascia tend to eliminate dead space. Drains are not used.

Defects about the vulvar area, laterally and posteriorly, are corrected by flap transplants. The length of the thigh is the area that is used for the available tissue. This allows for circular closure without tension. It permits earlier wound healing and is consistent in surgical practice.

We have had 8 cases of carcinoma of the vulva since 1949 treated by this one-stage process. Of these 8, two patients have lived more than 5 years and seem to be cured. One is in the fourth year of life and doing well. Two have lived 3 years plus and apparently are free of malignancy. Thus 5 of the 8 have had good results. It is of course too early and the series is too small to be significant.

There are 3 cases that are charged as failures. One patient is known to be dead from a melanoma (she died within one year following the operation). Two others have been lost to follow-up thus far and for statistical purpose must be considered dead.

We do not claim originality in this method of approach or the technique used, but merely wish to point out that it seems to have a better place than to allow the unclosed areas to heal by granulation.

DR. ISAACS (Closing).—I mentioned a few cases that were treated by means of radical vulvectomy followed by external irradiation. We do not follow that treatment any more. In the last 5 years our surgical excision has become more radical. We generally remove the inguinal nodes, the femoral nodes, and the nodes about the iliac vessels. Because we have an older age group, to be more radical than this does not seem justified.

As to the question regarding a better prognosis in granulomatous disease, we have not had enough cases in this part of the country to answer. I based my remarks on an article from Johns Hopkins Hospital published in *Obstetrics and Gynecology* in January, 1956. They had 7 cases with granulomatous lesions and only one with metastases. Otherwise, I have no further comments, except to add that in wound healing we also found difficulty in the inguinal areas. We have nothing to offer them at the moment except a little moral support.

SUBMUCOUS MYOMA IN THE NORMAL-SIZED UTERUS*

A Study of Endometrial Curettings for Its Detection

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WE HAVE encountered patients with abnormal uterine bleeding without demonstrable uterine or adnexal abnormality. In a number of these patients with normal-sized uteri, the pathologist noted the presence of smooth-muscle and fibrous tissue in the midst of endometrial curettings. This unusual finding aroused our interest in studying further all the slides in cases of dysfunctional uterine bleeding in the normal-sized uterus in which muscle tissue was reported. As material accumulated, we noted the frequency of this pathological entity in the absence of any other demonstrable disease. These bundles of smooth-muscle tissue could represent miniature myomas, located in the submucosa of the uterus.

The truth of this hypothesis was proved in studying 7 such uteri subsequently removed because of persistent bleeding. Small, round, single and multiple submucous myomas were found; on histological study the same characteristic findings noted in the curettings were encountered.

While the presence of miniature fibromyomas in the submucosa of the normal-sized uterus has been described in the literature previously, sufficient emphasis has not been placed on the finding of smooth-muscle and fibrous tissue in the endometrial curettings. Such muscle fibers were usually considered to be due to a too forceful curettage, rather than to the actual presence of myomas. We therefore must accept the presence of myomas and adenomyomas in the submucosa in a normal-sized uterus, small enough to escape detection by palpation of the curette and large enough to cause serious bleeding, requiring operative intervention.

We believe that this pathological entity is responsible for many cases diagnosed as dysfunctional uterine bleeding. We know of no previous work on this subject.

Material and Study

There were 27 private and 13 ward patients; 28 were white and 12 were Negro women. The youngest was 25, and the oldest was 58 years old. Twelve were nulliparous and 28 parous women.

The Type and Duration of Symptoms in the 40 Patients Studied.—Abnormal uterine bleeding was the major symptom (100 per cent) in all of the patients. It consisted of menorrhagia, metrorrhagia, menometrorrhagia, and

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postmenopausal bleeding. The duration of the uterine bleeding was up to six months in 28 patients, and intermittently from six months to six years in 12 patients. Twenty patients required blood transfusions; 16 patients had had previous gynecological operations.

Pelvic examination under anesthesia showed the uterus and adnexa to be of normal size, mobility, and consistency. The diagnostic curettage disclosed an irregularity in the uterine cavity in 9 of the patients, suggesting the possibility of a submucous myoma. The endometrial curettings were essentially normal: proliferative phase in 18 patients, secretory phase in 10 patients; 12 atrophic endometrial specimens were from patients over 50 years of age, with the exception of one patient who was 44.

Histopathology.—The pathological findings in the endometrial curettings were of four types: (1) smooth-muscle bundles, at times in small and often in sizable amounts; (2) muscle mingled with a large proportion of fibrous tissue; (3) fragments of pure fibrous tissue; and (4) smooth muscle containing endometrial glands.

We have felt justified in reporting the finding of these elements which without any further qualification could indeed suggest the presence of a protruding mass of myomatous tissue with or without fibrous degeneration. The mere mention of this finding does not imply by any means the sure diagnosis of submucous myoma, but it suggests the advisability of considering this diagnosis.

Certain qualifying circumstances increase or decrease the value of the finding of muscle in the curettings. If the muscle is partly mingled with fibrous tissue, we think that it is more likely to form a part of a fibroid than if it is pure smooth muscle. In our experience, the myometrium does not show a diffuse interstitial replacement by fibrous tissue except in the midst of a myomatous mass. If the partly fibrotic mass of muscle is found associated with fragments of endometrium, the diagnosis of submucous myoma is further strengthened. Without endometrium such a combination of muscle and fibrous tissue could well represent a fragment of cervical stroma which normally contains a good deal more fibrous tissue than the myometrium itself.

Pure fibrous tissue has been seen in at least two instances clearly associated with mucoid glands of cervical type. It is, therefore, to be suspected that fibrous tissue with no muscular component probably represents in most cases a portion of the cervical stroma. It is advisable to judge this in the light of how much cervical or endocervical mucosa is found in the curettings.

In some instances the fragments of muscle tissue contain endometrial glands with or without stroma embedded within them. This introduces the possibility of the diagnosis of adenomyosis, although it is not necessarily a true deep implant of endometrium that gives rise to this pattern each time. Submucous fibroids frequently encroach upon the basal endometrial glands. At any rate this does settle the question of the origin of the material as being myometrial and even submucous.

After due consideration of the question we find that although it is often difficult to establish an unequivocal diagnosis of submucous myoma on the basis of endometrial biopsy by the pathologist, nevertheless, a series of concurring elements leads to an almost inevitable conclusion that this is the diagnosis in some of the cases. And if to this is added the clinical impression, the value of the observation is considerably enhanced.

Discussion of Individual Cases

CASE 1.—No. 51115 (Fig. 1). This case illustrates the presence of combined smooth-muscle and fibrous tissue in moderate proportions. The amount of fibrous tissue was less

than that expected in cervix and more than is normally present in myometrium. The patient proved to have a submucous myoma as well as an adenomyoma.

CASE 2.—No. 51305 (Fig. 2). A case shown later to have an adenomyoma protruding into the endometrial cavity. Here the muscle was combined with a considerable amount of fibrous tissue. The association of the sclerosing muscle with endometrial glands constitutes excellent evidence of an abnormal process in the myometrium.

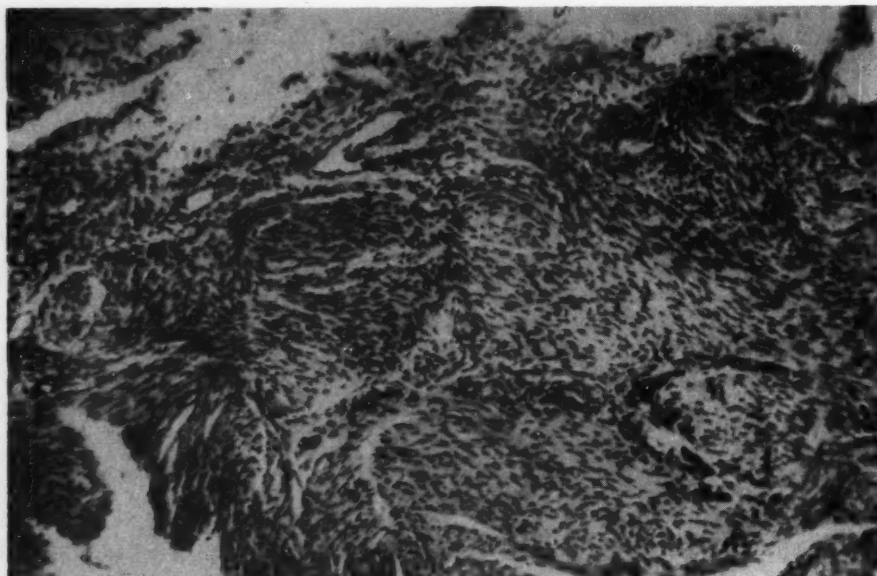


Fig. 1.—Case 1. Large fragment of apparently normal smooth muscle. (Hematoxylin and eosin. $\times 110$.)

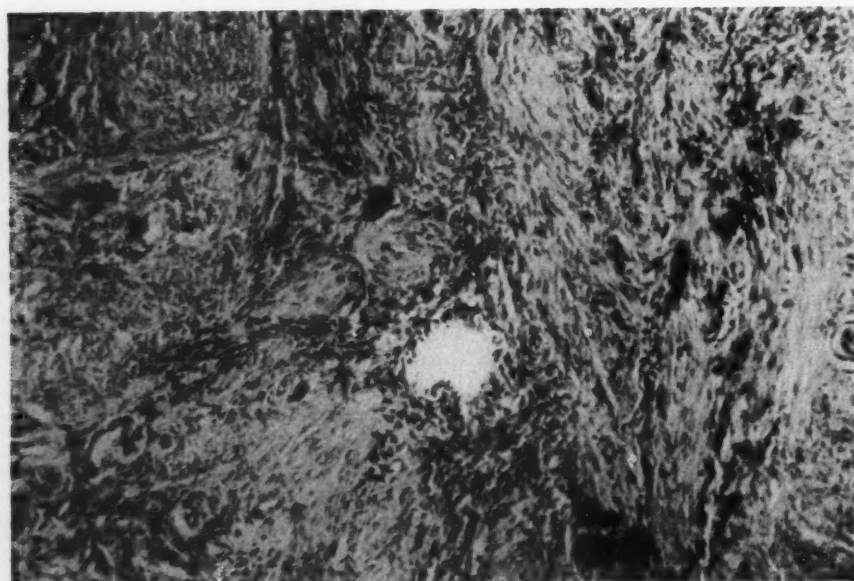


Fig. 2.—Case 2. Smooth bundles (lighter staining) separated by strands of fibrous tissue. A single distorted endometrial gland in the center. (Masson's trichrome. $\times 110$.)

CASE 3.—No. 53541 (Fig. 3). The endometrial curettings showed a striking amount of muscle with an estimated 15 to 25 per cent admixture of fibrous tissue. Most of the fragments were imbricated with endometrial glands, unequivocal evidence of the origin of the muscle tissue. The patient was shown to have a submucous myoma.

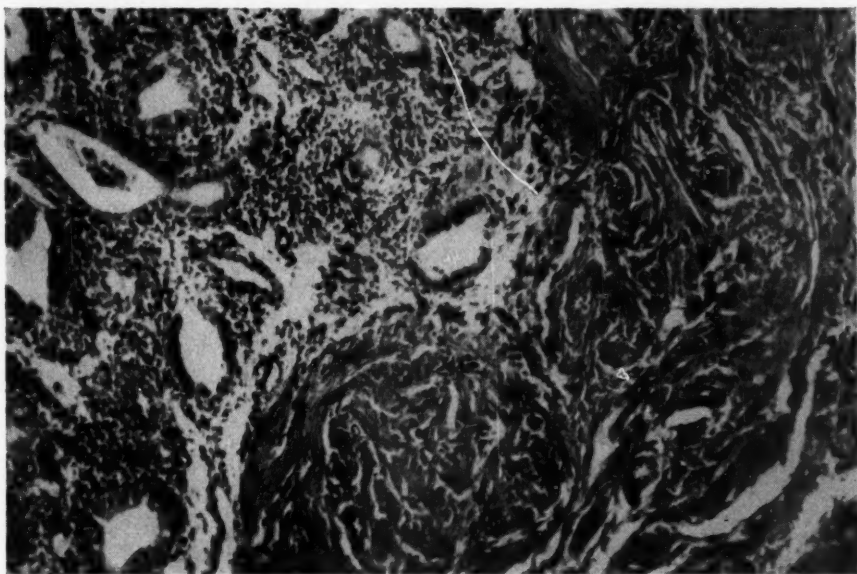


Fig. 3.—Case 3. Endometrium overlying rather elaborate whorls of smooth muscle with interspersed fibrous strands. (Masson's trichrome. $\times 110$.)

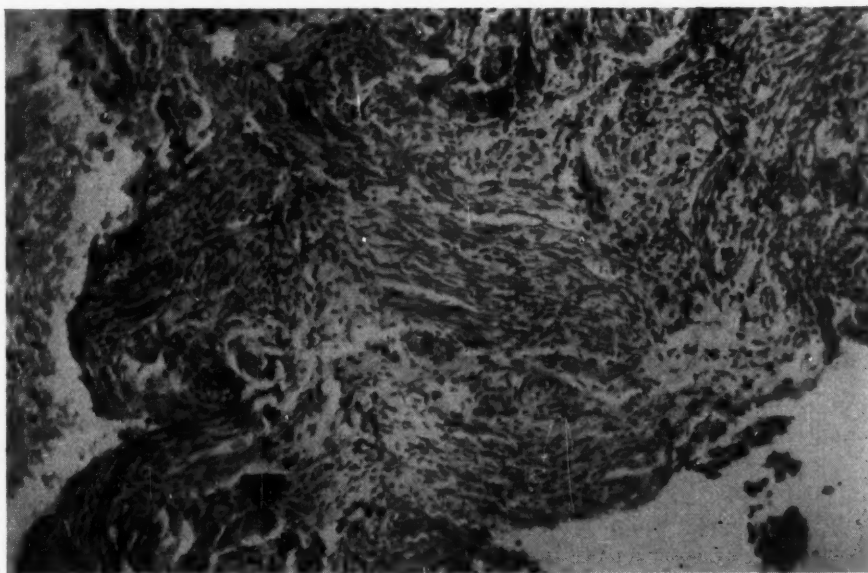


Fig. 4.—Case 6. Mingled fibrous and muscle tissue. (Hematoxylin and eosin. $\times 110$.)

CASE 4.—No. 54947. In this case in which a very minute submucous adenomyoma was found, the appearance was that of very cellular fibrous tissue with endometrial glands embedded in it. It was felt that this might represent fibrosis of the stroma except for the fact that other fragments of endometrium showed a normal stroma without fibrosis.

TABLE I. ABDOMINAL HYSTERECTOMY FOR PERSISTENT UTERINE BLEEDING (7 PATIENTS)

CASE	NAME	AGE	RACE	MARITAL STATUS	PARITY	ABORTIONS	NO. OF CURETTAGES PERFORMED	DURATION OF UTERINE BLEEDING PRIOR TO CURETTAGE	TIME LAPSE BETWEEN CURETTAGE AND HYSTERECTOMY	SYMPTOMS	SUBMUCOUS MYOMA SUSPECTED DURING CURETTAGE	MUSCLE AND FIBROUS TISSUE WITH ENDOMETRIAL SCRAPINGS	TYPE OF ENDOMETRIUM	TYPE OF OPERATION PERFORMED	HISTOLOGY OF THE REMOVED UTERUS
1.	E. H.	44	W	M	i	0	2	1 year	6 months	Menometrorrhagia	+	+	Atrophic	Total hyst.	Submucous adeno-myoma
2.	I. O.	53	W	M	0	0	2	1 week	6 months	Menorrhagia	-	+	Secretory	Total hyst.	Submucous myoma
3.	B. H.	51	W	M	ii	0	2	1 year	4 months	Menorrhagia	+	+	Proliferative	Total hyst.	Submucous myoma
4.	E. S.	50	W	M	0	0	1	4 weeks	1 month	Menometrorrhagia	-	+	Atrophic	Total hyst.	Submucous adeno-myoma
5.	B. R.	48	W	M	x	0	1	3 months	3 days	Menorrhagia	+	+	Proliferative	Total hyst.	Submucous myoma and adeno-myoma
6.	L. P.	41	Negro	M	ii	i	1	2 months	1 week	Menorrhagia	+	+	Proliferative	Total hyst.	Submucous myoma
7.	W. S.	39	W	M	0	iii	1	6 months	1 week	Menorrhagia	-	+	Secretory	Total hyst.	Submucous myoma

CASE 5.—No. 44461. The material was made up of almost equal proportions of endometrium and myometrium. The latter, seen in one place to be covered by thinned-out endometrium, showed the characteristic texture of a myoma with tightly whorled bundles of smooth muscle.

CASE 6.—No. 55331 (Fig. 4). One fragment of tissue included smooth muscle and normal endometrium as well as a large portion of muscle with hyperplastic endometrial glands and no normal endometrial stroma. This was interpreted as adenomyosis. There was a separate tag of fairly well-preserved smooth muscle, probably myometrium.

CASE 7.—No. 48791. There were two small fragments of smooth muscle; one of them intermingled with fibrous tissue and was attached to endometrium.

Masson's trichrome stain demonstrated fibrous tissue in the curetted fragments of myometrium.

Follow-up Report

A follow-up was obtained on 32 of the 40 patients, 12 of whom continued to have abnormal uterine bleeding after the diagnostic curettage. To date, 7 of these patients have had hysterectomies and one has been treated with intra-uterine radium. Four patients are under observation. The remaining 20 patients have been followed for six years and none has had abnormal bleeding.

The impression gained from the follow-up was that patients in whom uterine bleeding persists following a diagnostic curettage will probably continue to bleed until definitive treatment is instituted, as was evident in 8 of the patients already operated upon and the remaining 4 who are awaiting treatment.

An analysis of the 7 patients in whom the provisional diagnosis of submucous myoma was verified by hysterectomy (Table I) showed that 6 were white and one was Negro. They were 39 to 53 years old, 4 were parous, 5 were treated for menorrhagia and 2 for menometrorrhagia. The duration of the bleeding prior to the first diagnostic curettage was from one week to one year. The time lapse between the diagnostic curettage and the hysterectomy was from three days to six months. The endometrium was proliferative in 3 patients, secretory in 2 patients, and atrophic in 2 patients; muscle and fibrous tissue was found in the endometrial curettings.

Summary

1. Forty patients with submucous myomas and adenomyomas in the normal-sized uterus are presented.
2. The diagnosis was based on finding in the endometrial curettings smooth muscle, smooth muscle and fibrous tissue, fibrous tissue alone, and smooth muscle containing endometrial glands.
3. In 7 patients who underwent hysterectomy, the preoperative diagnosis from the curettings was confirmed in every case.
4. The endometrial pattern was normal in all of the patients presented.
5. On several occasions the diagnosis of submucous myoma was established on the second curettage.
6. Abnormal uterine bleeding was the major symptom of all of the patients; the tendency was toward menorrhagia.
7. Twelve patients persisted to bleed abnormally following the diagnostic curettage and in 20 patients there was no recurrence of abnormal bleeding.

Conclusions

1. The finding of fragments of muscle in the endometrial curettings is deserving of attention. In many cases the diagnosis could be overlooked by not putting more emphasis upon this microscopic finding.

2. Many patients with so-called dysfunctional uterine bleeding are actually bleeding from submucous myomas small enough to be missed by clinical examination and by curettage.

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Discussion

DR. HENRY BRODY.—Let us now examine critically the contention of the authors. They propose that from curettings it is frequently possible to make the diagnosis of submucous myoma. They assume that, when such myomas are present, the uterine bleeding is so explained. Both propositions should be discussed.

Can we safely infer from the presence of tiny fragments of muscle in curettings that these come from a submucous myoma? Drs. Zeigerman and Dapena have offered several criteria to distinguish between myometrium and myoma.

First, they suggest that the finding of endometrial glands admixed with muscle fibers indicates a submucous myoma. Although a curettement of a submucous myoma might produce such an intermingling, I would like to point out that the line of demarcation between myometrium and endometrium is frequently not sharp, and portions of endometrium (both glands and stroma) interdigitate with fibers of myometrium. Curettings might well include such scrambled portions without indicating a submucous myoma. Further controls are certainly necessary.

Second, and more important, the intermixture of fibrous tissue with muscle fibers is interpreted as representing fragments of myoma, and not myometrium. Dr. Dapena has recommended the use of a trichrome stain to emphasize the fibrous component. That fibrous tissue, showing more or less hyalinization, is frequently a component of the uterine myoma is well known; but fibrous tissue is not a necessary component of the uterine myoma. A certain proportion of submucous myomas would not be diagnosed if this criterion were strictly applied. On the other hand, does the presence of fibrous tissue intermixed with muscle necessarily prove myoma? Although pathologists have discarded the diagnosis "fibrosis uteri," fibrous tissue is not infrequent in the myometrium. Examination of routine hysterectomy specimens with a trichrome stain shows the frequency of subendometrial fibrous tissue, often showing some degree of hyalinization.

Drs. Zeigerman and Dapena's diagnoses of submucous myomas subsequently confirmed by hysterectomy in seven cases is provoking and stimulating. I would like to see both a greater number of cases and a larger series of controls. I would like to know how infrequently fragments of muscle and fibrous tissue are found in curettings from uteri in which no myoma can be demonstrated at subsequent hysterectomy. I think that is the crux of the matter, and it is a question which the essayists have not, as yet, completely answered.

Another question must be raised. Does the submucous myoma cause uterine bleeding? And if so, how? The answer to the first question is not a clear yes. Certainly, many uteri which contain submucous myomas do not bleed. It has been suggested that the same factors, endocrine perhaps, which make for myomas lead to uterine bleeding. If submucous myomas cause bleeding, what is the mechanism? There is little direct observation. It has been presumed that myomas somehow alter circulatory dynamics within the uterus, and particularly in the endometrium. The bleeding is usually hypermenorrhea, and not metrorrhagia. It has been suggested that the menstrual slough involves engorged veins in the periphery of the submucous myoma. It is interesting that myomas almost never

show venous engorgement. Sampson,¹ many years ago, demonstrated by injection studies that the vasculature of the myoma is almost without a venous component but is richly supplied with arteries.

Before tonight's meeting I asked Dr. Zeigerman if, on the basis of finding in a curet-tage muscle fragments which were diagnosed as submucous myoma, he would advise hysterectomy. His answer: "If the bleeding were sufficiently severe and did not respond to the usual therapeutic procedures," I would interpret as the properly conservative one. As these are the indications for hysterectomy for dysfunctional uterine bleeding, no objection can be voiced.

Dr. Zeigerman and Dr. Dapena have presented evidence that submucous myomas can be diagnosed from endometrial curettings. They have indicated that the evidence is still incomplete. I am sure that I, and other pathologists to whose attention this work is brought, will look with greater care at the muscle fragments we not infrequently find in curettings. All of us have, from time to time, suggested the possibility of myomas from such curettings. Dr. Zeigerman and Dr. Dapena have given us certain criteria, and the impetus to look more carefully. I am sure that with further study they will be able to bring more certain answers.

DR. VALDES-DAPENA.—Whenever fragments of muscle are included in a specimen of uterine scrapings, we may correctly say that a biopsy of myometrium has been obtained. It remains to decide whether this muscle is entirely normal, in which case it may or may not form part of a submucous myoma, or whether it shows characteristics which may lead one to suspect that the tissue in question comes from such a mass. We have not encountered significant degrees of fibrosis in normal myometrium and have never seen actual hyalinosis. On the other hand, fibrosis is the rule in myomas and hyalinosis occurs frequently. It should be possible, therefore, to identify a fragment of the myoma if it shows enough fibrous replacement or recognizable hyalinosis. It should be the policy of the pathologist in regard to this problem to be very conservative. We have, as a rule, only suggested the likelihood of the presence of fragments of myoma in the scrapings, but at times the appearance of the muscle tissue intermingling with substantial amounts of collagen and hyalinization and attached to fragments of endometrium has impressed us sufficiently to make us feel convinced that the curette performed a biopsy of a submucous leiomyoma. Whether or not this finding explains the abnormal bleeding usually present, it is worthy of being recognized and reported.

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INDUCTION OF HUMAN OVULATION BY INDIVIDUALIZED GONADOTROPHIN THERAPY IN TWO PHASES

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FOR conception to occur in women with amenorrhea or with anovulatory cycles, effective measures are necessary to induce ovulation. Induction of ovulation, though very important in treating the sterility patient, is extremely difficult.

Methods used in trying to induce human ovulation have comprised administration of gonadotrophins (a direct method), x-ray treatment, thyroid hormone and cyclic steroid therapy (an indirect method).

The results obtained by the administration of gonadotrophins (pregnant mare serum, pituitary plus chorionic, and chorionic plus pregnant mare serum) have varied with the different investigators. The indirect methods are by no means satisfactory in their effects and, so far, no really efficient method has been found. Accordingly, the present studies were made.

Method and Materials

The essentials of this method lie in (1) the administration of pregnant mare serum so as to make the follicle mature, (2) the administration of chorionic gonadotrophin to replace pregnant mare serum as soon as the maturation of the follicle is reflected by the fluctuations in the amount of cervical mucus.

1. When the cervical mucus is over 300 c.mm. in amount daily before the therapy, the follicles are presumed to be mature or almost mature and 1,500 I.U. of chorionic gonadotrophin is administered every other day for three days.

2. When the cervical mucus is below 300 c.mm. in amount before the therapy, in the anovulatory cycle the administration of pregnant mare serum is started on the tenth day of the menstrual cycle, while in the amenorrheic patient the therapy may be started at any time. In the case of longstanding amenorrhea or uterine hypoplasia, however, the administration of pregnant mare serum should be inaugurated on the tenth day after the start of withdrawal bleeding following the daily injections of 1 mg. of estradiol benzoate for ten days or the administration of 10 mg. of depot estradiol (estradiol valerianate) at a time.

The therapy in detail for repeated anovulatory cycles or amenorrhea consists of the daily administration of 1,000 I.U. of pregnant mare serum and for the occasional anovulatory cycle 500 I.U., both given intramuscularly for the first three days. From the fourth day, the injections are continued in the same way provided the cervical mucus is over 200 c.mm. in amount on that day. If the cervical mucus does not amount to 200 c.mm. on the fourth day, the daily doses of pregnant mare serum are increased to 1,000 I.U. or 1,500

I.U., respectively. Injections of pregnant mare serum are continued until as much as 3,000 I.U. is given daily, if the amount of the cervical mucus on the sixth day indicates the need. In both cases, the injections of pregnant mare serum are replaced by injection of 1,500 I.U. of chorionic gonadotrophin as soon as the cervical mucus amounts to 400 c.mm., followed by further injections of 1,500 I.U. every other day for two days.

Administration of pregnant mare serum should be discontinued in the following circumstances:

1. If ovulation is confirmed by the rise in the basal body temperature graphs. In such cases the progress should be watched for some time or 500 I.U. of chorionic gonadotrophin should be injected for four days.

2. If the cervical mucus is not increased in amount or ovulation does not occur in spite of the injection of pregnant mare serum in a considerably larger dose, e.g., if the cervical mucus fails to amount to 300 c.mm. despite 3,000 I.U. of pregnant mare serum daily for five consecutive days or its increase in amount remains entirely refractory to the injections of pregnant mare serum for ten consecutive days. In such individuals the ovaries are considered to be lacking in reactivity to pregnant mare serum, and this therapy should be replaced by some other.

3. If the ovary becomes unilaterally or bilaterally larger than a hen's egg in size accompanied by various subjective symptoms such as lower abdominal tension and pressure of the bladder, while the amount of cervical mucus remains less than 300 c.mm. during the course of therapy. If the amount of cervical mucus exceeds 300 c.mm. even though still under 400 c.mm., injections of chorionic gonadotrophin should be started to replace those of pregnant mare serum.

4. After the first series of treatments, regardless of the results, the injections are suspended for 40 days following the next cycle, and the cervical mucus is examined every day or every other day for evidence of possible spontaneous ovulation without hormone administration as evidenced from fluctuations in amount. If menstruation does not occur or anovulatory menstruation occurs during the course of the 40 days, the second series of treatment should be started.

Results

Results of this method of treatment are compared with those of other methods in Table I. "Prompt ovulation" and "delayed ovulation" refer to the ovulatory thermal shift of the basal body temperature within or beyond 48 hours following the administration of gonadotrophin.

As seen in Table I, in comparatively mild cases such as those with an occasional anovulatory cycle, ovulation was induced without exception by Method A. But in cases such as habitual anovulatory cycle or amenorrhea, Method B or C was effective in causing ovulation, Method A being mostly ineffective and Method C the most effective. In one case treated by Method C ovulation was not observed, and amenorrhea in this case was considered to be presumably due to the failure of the ovaries to respond to the pregnant mare serum—ovarian amenorrhea as it is sometimes called.

Comment

Since the study of Davis and Koff,¹ studies have been carried out by a number of researchers concerning the induction of human ovulation by pregnant mare serum, but the results vary considerably. Even in the favorable reports, the percentage of positive results is not always large. A pessimistic conception prevails today with regard to the induction of human ovulation by pregnant mare serum.

TABLE I. COMPARATIVE RESULTS FROM VARIOUS METHODS OF GONADOTROPHIN THERAPY

TYPE OF ANOVULATION	METHOD A (PMS* ONLY)	METHOD B (PMS + SYNABORIN*)	METHOD C (PMS + CG*)		METHOD D (PMS + CG) THE OTHER METHOD
			INDIVIDUAL TWO-PHASIC METHOD	METHOD	
Occasional anovulatory cycle	Prompt ovulation	Prompt ovulation	Prompt ovulation	Prompt ovulation	Prompt ovulation
	Delayed ovulation	Delayed ovulation	Delayed ovulation	Delayed ovulation	Delayed ovulation
	Ineffective	Ineffective	Ineffective	Ineffective	Ineffective
Habitual anovulatory cycle	Prompt ovulation	Prompt ovulation	Prompt ovulation	Prompt ovulation	Prompt ovulation
	Delayed ovulation	Delayed ovulation	Delayed ovulation	Delayed ovulation	Delayed ovulation
	Ineffective	Ineffective	Ineffective	Ineffective	Ineffective
Secondary amenorrhea					

*Synaborin, a gonadotrophic preparation containing animal pituitary gonadotrophin and chorionic gonadotrophin from human placenta, manufactured by Teikoku Hormone Mfg. Company, Tokyo, Japan.
PMS, pregnant mare serum gonadotrophin, Anteron (Schering A. G.) and Antex (Leo).
CG, Chorionic gonadotrophin, Primogonyl (Schering A. G.) and Physex (Leo).

For the induction of human ovulation gonadotrophin therapy, particularly pregnant mare serum, is considered theoretically and experimentally to be the most promising. The clinical results vary, presumably because of the difference in the methods of administration of the serum. No decisive conclusion has been reached as to the most rational and effective method for the induction of human ovulation by the administration of pregnant mare serum.

To administer pregnant mare serum followed by chorionic gonadotrophin, Hamblen's^{5, 6} one-two cyclic gonadotrophin therapy or Rydberg^{10, 11, 12} and Riiesfeld's⁹ method is theoretically more efficacious and the results are more favorable than administration of pregnant mare serum alone; this has been clearly shown by Hamblen's results and those in the present studies. When pregnant mare serum is administered alone, the ovulations induced are mostly delayed, while when pregnant mare serum is administered in combination with chorionic gonadotrophin as in the present studies ovulations were all prompt. To induce human ovulation by the giving of pregnant mare serum alone, the secretion of luteinizing hormone from the pituitary is considered an absolute requisite. When chorionic gonadotrophin is administered in addition, the secretion of luteinizing hormone may not always be necessary because of the luteinizing-hormone-like action of chorionic gonadotrophin. This appears possible in view of the results of Wahlen and the present studies, which indicate that, in the presence of the mature follicle, ovulation can be induced by the administration of chorionic gonadotrophin alone.

Up to this time, it has been held quite impossible to know whether or not the follicle is mature without laparotomy. In the present studies a method has been brought about for examining, although roughly, the degree of the maturity of follicles by determining the fluctuations in the amount of cervical mucus. When the cervical mucus aspirated amounts to 300 c.mm. the follicle is almost mature, when it attains 400 c.mm. it is fully mature.

It is now possible, without assaying the blood or urinary estrogen levels, to determine the degree of ovarian response to pregnant mare serum by examining the changes in the amount of cervical mucus.

In some women ovulation is easily induced by the injection of pregnant mare serum in comparatively small amounts (500 I.U. at one time), while in others it is entirely refractory even to large amounts (3,000 I.U. daily for several days). Ovarian reactivity to pregnant mare serum is largely dependent upon the individual degree of disorders present or upon the ovarian cycle.

By the present method daily changes in the ovarian reactivity to pregnant mare serum can be promptly judged in the consultation room by checking the cervical mucus and the basal body temperature every day, and from these data the kind and the dosage of gonadotrophin to be administered each day can be reasonably adjusted. When the maturity of a follicle is thus ascertained, pregnant mare serum is replaced by chorionic gonadotrophin so that ovulation occurs. We consider this method the most rational so far used.

The administration of pregnant mare serum and chorionic gonadotrophin is not always without ill effects. In the present experiments enlargement of ovaries with tension in the lower abdomen and the symptom of pressure on the bladder were encountered in two cases. This enlargement of the ovaries began with the administration of pregnant mare serum and was intensified by chorionic gonadotrophin, but a decrease in size followed the discontinuation of its administration. The original size was regained by the beginning of the next menstrual cycle.

Another ill effect of pregnant mare serum that should be taken into account is the formation of antihormones. In that pregnant mare serum is a

kind of heterogenous protein, it is fairly certain that by its injection anti-hormones may be formed in the human body, as has actually been evidenced by the studies of Ostergaard⁸ and Leathem.⁷ Our method appears to be capable of limiting the formation of antihormones to a minimum.

Summary

1. It has been pointed out that the maturation of a follicle is indispensable for ovulation.

2. A new method has been given by which the degree of maturation of follicles can be ascertained from variations in the amount of cervical mucus.

3. The administration of chorionic gonadotrophin alone is sufficient to induce ovulation in cases of failure secondary to lack of luteinizing hormone in spite of maturation of a follicle.

4. In cases where follicular development was considered defective, ovulation has been induced by administering pregnant mare serum daily and replacing it by chorionic gonadotrophin as soon as maturation was detected by daily examination of the cervical mucus.

5. If the cervical mucus did not increase in amount in spite of the administration of pregnant mare serum, induction of ovulation failed.

6. On the basis of all such experimental results, a new and most effective method for inducing human ovulation has been worked out. This method, a modification of that of Rydberg and Riiesfeld differs from others in that individualized therapy is stressed.

We wish to express our hearty thanks to Dr. Toshio Hasegawa, Professor of Obstetrics and Gynecology, University of Tokyo School of Medicine, for his kind help in the present studies.

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THE ACCURACY OF GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY REPORTS IN A SMALL HOSPITAL

A Review of Two Hundred Pathology Reports

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THIS study was prompted by the reception, during a period of more than 25 years, of many pathological reports that immediately were recognized as being in error, or were subsequently discovered as erroneous as a result of the clinical course of the patients. Some of the incorrect reports have been of serious import to the patients. Since we feel that all gynecologists have had similar experiences, it seems unnecessary to quote examples to illustrate the range of importance germane to the accuracy of pathological reports.

Serious legal problems may arise, due to failure to include description of all pathological lesions in the hospital records. A pathological report describing even a small myoma in the uterus may protect a surgeon from possible legal action. The pathologist bears responsibility and is remiss in his duty if he fails to report upon all tissue received in the laboratory, although he may not be responsible for errors of interpretation.

Since not only the surgeon, the nurse, the technician, but also the pathologist are human, it is not unexpected that an occasional error will be found in pathological reports. What is the incidence of such errors? We are unaware of any available reports or studies of this nature. This investigation was begun in order to determine whether the number of such errors is significant and what types of error may be made, and, finally, what precautions should be formulated for their prevention. There is not available, and probably cannot be determined, exact information concerning the percentage of error of interpretation in routine histopathological study of microscopic preparations of surgically excised tissue. While pathologists may differ in their criteria for the diagnosis of acute appendicitis,¹ no great errors should arise when the pathological laboratory receives a single structure such as a gall bladder, appendix, excised stomach, kidney, segment of bowel, etc. However, when presented with a complete uterus, both ovaries, and both Fallopian tubes—structures capable of exhibiting a great variety of lesions, often incipient—the possibility of error and of nonrecognition is greatly increased. Surprisingly, even in reporting upon comparatively simple tissue such as that obtained by curettage, errors occur. It is thus seen that in this respect the problem differs greatly for the gynecologist in contrast to the general surgeon. That there is a definite percentage of such error is conceded. Brewer and Miller² alluded to this problem in discussing postmenopausal uterine bleeding.

They mentioned how specimens are duly examined in the department of general pathology and also in the gynecological pathology laboratory, resulting in more complete diagnoses, since at least double the number of blocks are examined and described. Endometrial carcinomas have been missed in one laboratory but picked up by the other. However, there may be other sources of error in the pathological reports as returned to the surgeon.

In this study no effort will be made to appraise the first source of error, i.e., the interpretation of the microscopic sections, since this would require a review of all gross and microscopic specimens by a panel of pathologists. This paper is concerned primarily with the other sources of error encountered. These are many and some are the fault of the surgeon. Failure to secure adequate tissue for biopsy, to assay the best site from which to secure the biopsy, and even failure to see that the specimen has been placed in the collection basin or bottle may be laid at the surgeon's doorstep.

It is not unknown for specimens to be lost in the operating room. I have seen in one hospital an untrained worker, originally hired for cleaning purposes, picking curettings from gauze and transferring them into a bottle. Even a nurse may think a small piece of tissue not worthy of laboratory study, especially if there is a huge ovarian cyst or large myoma which catches her eye.

On occasion, errors may be due to confusion arising in the labeling of the specimen, so that tissue is sent to the laboratory with the wrong patient's name attached. Although difficult of proof, this has occurred recently. Two dilations and curettages were performed, the second operation immediately following the first one. When the pathological reports were received, it was apparent that the report from Patient A fitted perfectly with the findings and history of Patient B, but could not be correlated with Patient A. This perplexing situation was discussed with the pathologist, who of course could only repeat that the specimens when received were so labeled and the report was correct for the individual specimens. The only solution of the problem would have been a repetition of the operation on at least one of the patients. While this error would arise most frequently in the operating suite, it conceivably could occur in the laboratory.

Having made a description of the gross specimen, the pathologist proceeds to select portions for histopathological examination. Even the most experienced and astute pathologist may neglect to obtain a section which could reveal the pathological condition. The preparation and study of serial sections of every uterus, ovary, and Fallopian tube is admittedly a Utopian situation, unlikely to exist in the near future in most small institutions, but until this goal is achieved carcinomas and other pathological lesions will be overlooked and erroneous reports will be returned.

It is probably impractical in small laboratories for the pathologist, with limited technical help and no residents in training, to employ other than routine staining techniques. Without these, however, many pathological entities must go unrecognized and obscure and rare tumors be inaccurately labeled. It is not routine, in this institution, to stain specimens for elastic tissue. Again,

being human, pathologists tend to look for certain diseases and take note of others only when they are very prominent. In a recent period of two weeks a relief pathologist reported three uteri as containing adenomyosis, yet it is seldom that our reports label the uterus as so involved. While this may have been coincidence, in reviewing many reports it became apparent that one or two of the pathologists were prone to find and report adenomyosis, whereas it was a rare finding by the other pathologists.

Material

Two hundred pathological reports from one hospital were reviewed. All reports were on private patients and taken from office files. The cases reviewed were taken without selection alphabetically, starting with A, and comprising reports from 1948 to and including 1954. During the years of this study eleven pathologists have rendered reports at this hospital. At the beginning of the period of time covered our pathologists were not resident in the community and were on a very haphazard basis, spending one or two mornings or afternoons a week at the hospital. The present incumbent serves two hospitals in the community. When he is absent or on vacation, substitutes are employed. The large number of pathologists concerned in this study we believe enhances any merit therein.

It is admittedly difficult to be impartial and objective, but every effort has been made to consider the pathological report as correct in any doubtful case. In reviewing these reports we have tried to avoid quibbling and bias as known to statisticians. Each pathological report was compared with the findings at operation as recorded on the operative record and, when necessary, with the case history. If the report described or a diagnosis was given of the main pathological condition present, it was classed as being in complete agreement with the operative findings; e.g., if myomas were reported, but no mention made of a small area of endometriosis in an ovary or of an occluded fimbriated end of a Fallopian tube, no disagreement was recorded. Failure to report hypertrophied or severely lacerated cervixes was not considered disagreement, although we feel they should be recorded by the pathologist. On the other hand, when no large uterine masses or large ovarian cysts were present in the specimens, the report was considered to be in disagreement if small myomas were not recorded by the pathologist. Certainly, a small myoma may produce symptoms, while a fairly large one be asymptomatic. It will be noted that in some instances the pathological report was amended. These cases were considered to be in disagreement because, if a review had not been requested, the chart would have contained an error in the pathological diagnosis. Unfortunately, the pathologist could not always be located and requested to review the report and microscopic findings, and in the first years of this study a report at variance with the operative findings was often shrugged off as not mattering too much as long as the operative record disclosed the true findings. Had more requests for review been made, undoubtedly the percentage of error in the initial reports would have been greater.

Of the 200 cases reviewed, absolute agreement with operative findings and pathological reports was noted in 174 (87 per cent). Disagreements totaled 26 (13 per cent). Of the 200 cases 5 (2.5 per cent) were amended upon request, leaving 21 (10.5 per cent) cases which finally were in disagreement. In 12 (6 per cent) cases there was failure to report on all tissues removed; in 2 (1 per cent) of these cases amended reports were obtained upon request.

TABLE I. ERRORS IN PATHOLOGICAL REPORTS

CASE NUMBER	PATHOL- OGIST	REPORT AMENDED	TISSUE UNRE- PORTED	REMARKS
1. E. A. S-1528-52	A	Yes	Yes	Original report did not include microscopic findings of curettings, nor endometriosis of ovary. Upon request a second report described both.
2. V. A. S-427-51	A	No	Yes	Cervix not examined. Definite endometriosis of densely adherent ovary not reported. Adenomyosis reported moderately severe.
3. R. A. S-527-49	C	No	Yes	A 4 cm. thin-walled mass removed intact by curette was unreported. This may not have reached laboratory despite interest expressed in operating room.
4. M. B. S-831-51	A	No	Yes	Cervical polyp not mentioned in report.
5. M. B. S-659-51	A	No	Yes	Small excised myoma not described. Ruptured ovarian cyst described as ovary with smooth surface.
6. G. B. S-599-51	A	Yes	Yes	Small myoma not reported. Upon request this was included in report. Primary pathological finding was tubal gestation.
7. S. B. S-80-51	B	No		Typical implants of endometriosis present in peritoneum. Ovarian cyst reported as follicular. Patient later required second operation for recurrence of endometriosis.
8. A. B. S-1315-52	D	No	Yes	Cervical polyp not reported.
9. S. B. S-960-52	A	No		Previously operated upon for endometriosis. Diffuse peritoneal implants and remaining ovary excised because of apparent endometriosis. Not confirmed by pathologist.
10. J. B. S-3078-54	E	No		Very large amount of placental tissue removed at curettage reported as secretory endometrium with decidual reaction and endometritis.
11. J. B. S-2849-54	A	No		Incomplete rupture of uterus with huge defect reported as "uterus—post gravida."
12. R. C. S-2429-53	F	No		A large serous cyst was ruptured during removal. Reported as intact ovary showing a corpus luteum and stromal hyperplasia.
13. L. C. S-951-52	A	Yes		First reported as proliferative (follicular) endometrium. Upon request, re-examined and reported "microscopic examination of more tissue revealed small portions of decidual tissue." At operation tissue appeared typical of formed placental tissue.
14. E. C. S-605-51	A	No		Multiple small myomas not reported.
15. E. C. S-3726-54	G	No		Typical placental tissue reported as florid-type secretory endometrium.

TABLE I—CONT'D

CASE NUMBER	PATHOL- OGIST	REPORT AMENDED	TISSUE UNRE- PORTED	REMARKS
16. G. D. S-439-51	A	No		Clinically typical of ovarian endometriosis. Report stated areas of pigmentation with hemosiderin, but no endometrial glands or stroma.
17. E. D. S-3900-54	A	No	Yes	Peritoneal cysts unreported, also peculiar 3-4 cm. mass contained in ovary.
18. M. D. S-2607-54	A	No	Yes	Cervical and endometrial polyps unreported.
19. G. D. S-2442-53	F	Yes		Diagnosis of adenomyosis made at previous operation not made in second operation. Ovary first reported as follicular cyst, then amended to: "Sections of ovary while not diagnostic of endometriosis are certainly compatible with such a diagnosis."
20. F. E. S-567-51	A	No	Yes	Myoma not reported. Clinical ovarian endometriosis labeled perioophoritis; definite bilateral hydrosalpinx labeled perisalpingitis, chronic.
21. L. F. S-302-51	A	No	Yes	Biopsy of endometriosis peritonei unreported.
22. V. F. S-593-50	B	No		Clinical endometriosis and adenomyosis labeled salpingitis isthmica nodosa, stromal hemorrhage in ovaries.
23. R. F. S-187-49	C	Yes	Yes	Report amended upon request to include presacral nerve.
24. J. F. S-3848-54	A	No		Moderately large polyps reported merely as endocervical tissue.
25. M. F. S-3641-54	A	No	Yes	Endometrial polyp reported as endocervical polyp. Cervicitis not reported. (Biopsy taken.)
26. R. F. S-3579-54	H	No		Very diffuse implantations of endometriosis peritonei. Ovary densely adherent with pockets of chocolate-colored material rupturing during removal; ovary lost all recognizable form, but was reported as 4 by 2 by 0.7 cm. This size ovary could not have contained a small fraction of the chocolate contents which escaped during mobilization. Adenomyosis reported, but not endometriosis of ovary.

TABLE II. INCIDENCE OF ERROR IN 200 PATHOLOGICAL REPORTS

	TOTAL	%
Total cases reviewed	200	100
Errors in pathological reports	26	13
Agreement or no significant error	174	87

Endometriosis

The greatest discrepancy arose, as was expected, in cases involving endometriosis. Of the 200 cases reviewed 97 (48.5 per cent) were laparotomies in

which tissue was removed where conceivably endometriosis might be found. Cesarean hysterectomies were excluded. Of these 97 laparotomies there were 35 cases (36.1 per cent) in which a clinical diagnosis of endometriosis was made. In a very few cases, while the clinical diagnosis was unquestionable, no biopsy was taken because of technical reasons. Of the 35 clinical cases of endometriosis there were 10 (28.5 per cent) in which the findings at operation showed a definite endometriosis, such as peritoneal implants or adherent ovaries with chocolate cysts which, perforce, ruptured during mobilization but in which endometriosis was not described by the pathologist. In instances where the pathologist was given tissue in which he could not be expected to find endometriosis, failure to report it was not considered a disagreement. It should be noted that of the 97 laparotomies reviewed endometriosis or adenomyosis was reported by the pathologist in 5 cases (5.2 per cent) in which the operative diagnosis did not record it. It is realized that often, in large ovarian cysts that are unquestionably perfect examples of endometriosis, some pathologists will not make this diagnosis, depending upon their criteria for diagnosis of endometriosis. Sturgis and Call³ point out that the implants of endometriosis peritonei may become strangled by organization of fibrous tissue and endometrium may not be demonstrable. Some pathologists will accept the presence of hemosiderin as proof of endometriosis; others require demonstration of either glands or stroma and some insist on both glands and stroma.

Brewer and Maher,⁴ in an article on conservatism in endometriosis, stated that histological examination of the removed tissue does not always show endometriosis, even though it is present—especially in cases of endometriosis of the uterosacral ligaments and posterior surface of the uterus—since these lesions promptly lose their characteristic color and appearance after removal of the uterus, and the pathologist does not take blocks of tissue from this region. The same authors stated that errors frequently result from study of only a few blocks of tissue from the wall of a blood-filled cyst of the ovary and attempting to make a diagnosis upon study of this infinitesimal portion of the tumor.

It is apparent why a biopsy of the peritoneum or of a uterosacral ligament may be reported as not showing endometriosis. On occasion, however, an amended report, based upon additional sections or further search, has been returned with endometriosis as an added diagnosis. In 3 of the cases the pathologist included a diagnosis of endometriosis followed by a “?”, emphasizing the difficulty often encountered in establishing this diagnosis. Similarly, in an occasional report, a cystic structure could not be recognized by the pathologist as of tubal or ovarian origin.

TABLE III. INCIDENCE OF ENDOMETRIOSIS IN 97 LAPAROTOMIES

	TOTAL	PER CENT
Laparotomies excluding cesarean hysterectomies	97	100
Clinical diagnosis of endometriosis	35	36.1
Endometriosis or adenomyosis confirmed		
by pathologist	18	18.6
Endometriosis probable to pathologist	4	4.1
No biopsy made	2	2.1
Biopsy made but not reported	1	1.0
Endometriosis present but not reported		
by pathologist	10	10.3

Avoidance of Errors

It is the surgeon's responsibility to choose the proper area for biopsy; to make certain that adequate material is removed; to insure proper preparation of blocks. Probably, he must also share in the responsibility for ascertaining

that small specimens reach the container in which they are to be conveyed to the laboratory. Possibly, small, individual, sterilized bottles as a part of the setup on the instrument table would be desirable rather than putting all tissue—both large organs and small biopsy specimens—in a large basin in which the smaller bits of tissue may be overlooked, due to clinging to the larger structures.

It should be the responsibility of the operating room nurse or supervisor to see that no tissue disappears, except into the proper containers and to be absolutely certain that each container is properly labeled with the patient's name and to insure rigidly that no mislabeling occurs, to avoid patient-specimen confusion. This procedure should not be entrusted to untrained help.

The responsibility of the pathologist and his technicians is great. We hesitate to offer suggestions to our busy and overworked confreres. To suggest more blocks, special stains or serial sections, while most desirable, is perhaps impractical in a small institution which is understaffed. We can, however, when our suspicion is aroused, request review of the slides and cutting of additional blocks. One suggestion seems pertinent: We think it would reduce the number of errors if the pathologist would at some time during the course of each operation visit the operating room and inspect the opened abdomen or the visualized cervix, make a note of the pathology in situ, and decide and note where the sections will be cut. This program might prove to be very instructive to the younger pathologist whose training has included little surgery.

Summary

1. Two hundred pathological reports were reviewed. The reports were unselected and comprised the first 200 as alphabetically filed in office records.

2. Before amended upon request for review by the pathologist, the error was 13 per cent; subsequently, amended reports reduced the error to 10.5 per cent. The number of amended reports is small, but comprises 19.2 per cent of the cases considered as originally in error. This constitutes admitted error by the pathologist of 5 reports in 200 cases, or 2.5 per cent. These figures must be considered with respect to the fact that requests for review were seldom made because of inaccessibility of the pathologist during the first years of the study.

3. The problem of error in pathological reports is unquestionably greater in gynecology than in general surgery.

4. The sources of error in pathological reports are noted.

5. Suggestions are formulated to minimize erroneous reports.

6. The errors due to misinterpretation of microscopic slides are not calculated in this study and if capable of determination would add an unknown additional percentage of error.

References

1. Rosset, E. M., and Conston, A. S.: *AM. J. OBST. & GYNEC.* 61: 1136, 1951.
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3. Sturgis, H. S., and Call, B. J.: *AM. J. OBST. & GYNEC.* 68: 1421, 1954.
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COMPARATIVE CLINICAL EVALUATION OF POSTPARTUM OXYTOCICS

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MANAGEMENT of the immediate postpartum period, justifiably designated "the fourth stage" of labor,⁹ is a vital concern of the obstetrician. The control of hemorrhage during this important period through the use of oxytocic preparations has won wide acceptance. That these uterotonic drugs have a place in our armamentarium is appreciated, but it has become more and more apparent, with closer clinical observations, that they are not without significant untoward side actions. It was with this in mind that the present study was undertaken for the purpose of controlled clinical evaluation of the various oxytocic preparations currently available and in use.

Methods and Materials

A series of 1,221 consecutive patients delivered on the ward service of the Sloane Hospital for Women was studied. These were divided into five unselected groups with reference to the oxytocic drug administered post partum: (1) a control group of patients who received no medication post partum except as indicated, (2) a group who received oxytocin (Pitocin, Parke, Davis), 10 units intramuscularly, (3) those who received ergonovine maleate (Ergotrate maleate, Lilly), 0.2 mg. intramuscularly or intravenously, (4) those who were given methylergonovine tartrate (Methergine tartrate,* Sandoz), 0.2 mg. intramuscularly or intravenously, and (5) a group who received dihydroergotamine methanesulfonate (DHE-45,* Sandoz), 1.0 mg. intramuscularly after delivery of the placenta. The patient material for each group was randomly selected on a temporal basis.

Data were elicited in each case with reference to blood pressure recordings before and during pregnancy and labor, duration of labor including the length of the third stage, sedation and anesthesia during labor and delivery, trauma, estimated blood loss, and occurrence and degree of nausea and vomiting post partum. Blood pressure and pulse observations were made at 5 minute intervals for one hour after delivery. Ante- and postpartum hemoglobin levels were determined. The responsiveness of the uterus to the medication given was noted, and atony reported.

Patients in whom adequate observations were not obtained, for whatever reason, were deleted from the study. This left a total of 894 cases, including 177 controls, 214 in the oxytocin group, 210 receiving ergonovine, 167 methylergonovine, and 126 dihydroergotamine. The small number in the last group reflects the very apparent clinical impression that atony and postpartum hemorrhage were not infrequently associated with the use of this drug. It was on this account that its study was not continued.

*Methergine tartrate and DHE-45 were supplied by Nicholas J. Pappas of the Pharmaceutical Division of Sandoz Chemical Company, Hanover, N. J.

Results

In order to ascertain whether the five groups were truly comparable, so that only the single variable of the oxytocic agent employed might account for any differences found, they were individually and collectively examined with regard to such factors as age, parity, gestational age, incidences of precipitate and of prolonged labors, of prolonged third stage, of heavy and of light analgesic-sedative effect, of types of anesthesia employed, and of trauma inflicted.

The mean age incidence ranged from 26.2 to 27.2 years among the groups, distribution of 5 year increments being nearly identical in each. Parity averaged from 1.2 to 1.4, the distributions again being very nearly equal throughout the groups. Gestational age at delivery was likewise comparable.

The incidence of precipitate labors (under 2 hours) varied from 4.8 to 10.7 per cent; of prolonged labors (over 20 hours in primiparas, 12 hours in multiparas) from 12.7 to 17.8 per cent; of prolonged third stage (arbitrarily over 10 minutes) from 6.6 to 13.1 per cent. Heavy sedation effect was noted in from 3.2 to 12.4 per cent; light sedation occurred in from 20.5 to 29.9 per cent. The type of anesthesia utilized in the groups included 32.4 to 50.9 per cent conduction (spinal, caudal, epidural, or pudendal block) and 48.6 to 62.9 per cent general (nitrous oxide and cyclopropane largely).

Trauma included 61.9 to 71.0 per cent episiotomies, and 2.4 to 4.0 per cent second-degree lacerations. The incidences of third-degree, cervical, and sulcus lacerations were negligible (0.1, 1.2, and 1.1 per cent, respectively), as was the incidence of midforceps procedures (1.2 per cent over-all).

In none of the groups was there found to be a factor which occurred with significantly different frequency from the over-all incidence or that of the control group. Of borderline significance (by chi-square analysis) was perhaps the unusually high frequency (50.9 per cent) of patients receiving conduction anesthesia in the oxytocin group.

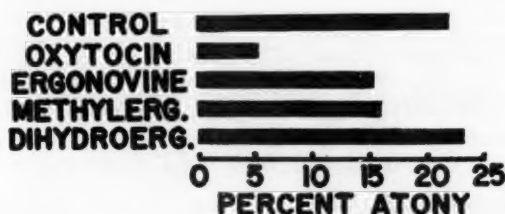


Fig. 1.—The occurrence of postpartum uterine atony in association with the use of uterotonic agents.

Uterotonic Activity and Hemorrhage.—

Control: Twenty-two per cent of the control group (Fig. 1) exhibited uterine atony following delivery of the placenta. Most of these required the administration of one of the oxytocics with which we are here concerned, as well as other measures, particularly massage, to stimulate the uterus to contract and thereby control or prevent bleeding. It was apparent, at least in the 78 per cent untreated in this group, that routine use of a uterotonic agent post partum was by no means essential.

In view of the fact that estimations of blood loss are at best quite poor, little importance should be attached to the actual ascribed amount which in this group averaged 228 ± 5 c.c. Nevertheless, grouping into 250 c.c. increments seemed justified. Accordingly, it was found (Fig. 2) that in the control group 58.8 per cent lost under 250 c.c., 39.2 per cent lost between 250 and

499 c.c., and 2.1 per cent lost over 500 c.c. Hemoglobin determinations before and after delivery were found to be of no value as a check on estimated blood loss.

Oxytocin: Atony was demonstrated in only 5.1 per cent of the oxytocin group, a remarkably significant infrequency, indicating the probable effectiveness of this drug.

Mention has been made of the deviation of this group from the others in the occurrence of excessive numbers of patients who received conduction-type anesthesia. Correlated with this were an unusually small number who received general anesthesia. This may have been a factor in producing the remarkable rarity of atony, because, as will be discussed below, general anesthesia seems to be significantly closely associated with atony and hemorrhage.

Estimations of blood loss averaged 217 ± 8 c.c., a value not significantly different from that of the control group. The groups with 250 c.c. increments of blood loss were likewise not dissimilar in distribution frequency from the controls.

Ergonovine: Among the patients who received ergonovine maleate post partum, 33, or 15.7 per cent, were observed to have uterine atony which required further therapy. This is a reduction in the absolute incidence, but is found not to be statistically significant when compared with the incidence in the control group of patients.

The drug was administered intramuscularly in 174, these exhibiting an incidence of atony of 15.5 per cent; and intravenously in 36 with atony in 16.7 per cent. It is justified, from these data, not to implicate the route of administration.

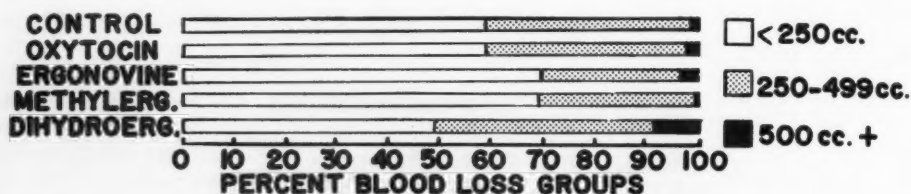


Fig. 2.—Incidence of blood loss at delivery by 250 c.c. increments according to the oxytocic administered.

Blood loss estimations, similarly, averaged a statistically insignificant 216 ± 14 c.c. On the other hand, a total of 70.0 per cent were estimated to have lost under 250 c.c.; 26.2 per cent between 250 and 499 c.c.; and 3.9 per cent over 500 c.c. These values differ considerably from those of the controls, there being far fewer patients with noteworthy hemorrhage among those who received ergonovine.

With reference to the route of administration, significant blood loss (over 250 c.c.) was exhibited in only 19.0 per cent of those to whom the drug was given intramuscularly post partum; in 36.2 per cent of the others (intravenous series). This tends strongly to suggest that the intramuscular route is the more efficacious. It is to be noted, however, that this subgroup received significantly more conduction anesthesia, a factor which may indeed influence the incidence of atony and blood loss.

Methylergonovine: Sixteen and eight-tenths per cent of the patients given methylergonovine tartrate post partum exhibited significant uterine atony, certainly fewer than in the control group, but not significantly different. By the intramuscular route (in 143), the drug was associated with atony 17.5 per

cent of the time; intravenously (in 24), 12.5 per cent. This illustrates a lack of real difference, in this particular respect, between these methods of administration.

Noteworthy blood loss occurred in 30.2 per cent—between 250 and 499 c.c. in 29.3 per cent and over 500 c.c. in 0.9 per cent. The remainder, 69.8 per cent, were estimated to have lost under 250 c.c. at delivery. No over-all differences were noted between intramuscular and intravenous administrations. Average blood loss was 203 ± 7 c.c., significantly less than that of the control group. This perhaps illustrated that the drug is effective in curtailing hemorrhage, both in frequency (0.9 per cent incidence) and in actual amount lost.

Dihydroergotamine: Atony characterized 23.0 per cent of the patients who received dihydroergotamine. Fifty-one per cent were felt to lose significant quantities of blood at delivery: 43.0 per cent 250 to 499 c.c. and 8.0 per cent 500 c.c. and over. Only 49.0 per cent lost less than 250 c.c. Mean over-all estimated blood loss was 255 ± 14 c.c., a large figure whose difference from that of the control group is of borderline significance. Nevertheless, the clinical impression that the use of the drug is of little or no merit as a uterotonic agent in preventing atony and combating hemorrhage is upheld.^{15, 17, 19}

This confirms the pharmacological action ascribed to hydrogenated preparations of ergot derivatives, namely, that they are biologically opposite in action to the parent substance, and may indeed block the action of the latter.^{6, 7, 14} This blocking action was implicated on the several occasions when the response expected from other oxytocics used subsequently, in particular oxytocin, was not immediately forthcoming. The method described by Leff¹⁶ notwithstanding, therefore, the use of dihydroergotamine, with or without oxytocin, as a postpartum oxytocic cannot be condoned. It is possible that its relaxing qualities can be put to effective use in other circumstances, but that is not the concern here.

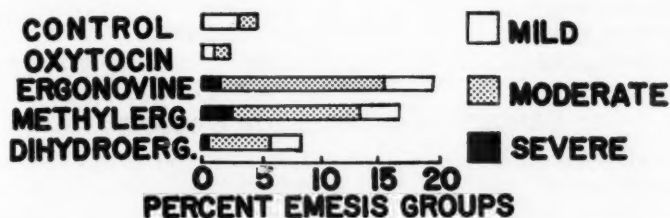


Fig. 3.—Frequency of postdelivery nausea and vomiting following the several drugs studied.

Nausea and Vomiting.—

Evaluation of the side actions of the drugs in question began with the determination of "normal" frequency of occurrence of nausea and vomiting post partum. An over-all incidence (Fig. 3) in the control group of 4.5 per cent was found, made up of 1.7 per cent mild (retching only), 2.8 per cent moderate (nausea and one or two episodes of vomiting), and none severe (intractable nausea and vomiting).

Comparable incidences were noted in the oxytocin group: 0.9 per cent mild and 1.4 per cent moderate, over-all 2.3 per cent.

In the ergonovine group, nausea and vomiting occurred in 19.5 per cent, a significant frequency. This was composed of 4.3 per cent mild, 13.3 per cent moderate, and 1.9 per cent severe. Breakdown by route of administration showed impressively more frequent and more severe nausea and vomiting following intravenous injection, significant (other than mild) emesis occurring in 19.5 per cent as against 14.4 per cent after intravenous and intramuscular administration, respectively.

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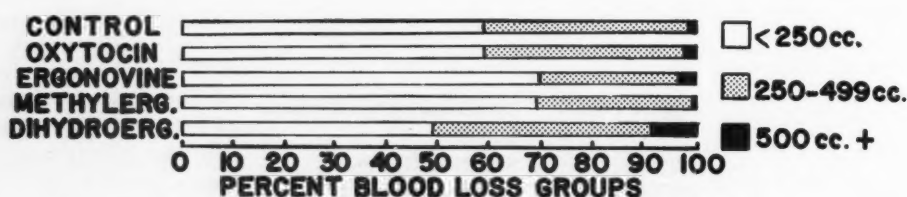


Fig. 2.—Incidence of blood loss at delivery by 250 c.c. increments according to the oxytocic administered.

Blood loss estimations, similarly, averaged a statistically insignificant 216 ± 14 c.c. On the other hand, a total of 70.0 per cent were estimated to have lost under 250 c.c.; 26.2 per cent between 250 and 499 c.c.; and 3.9 per cent over 500 c.c. These values differ considerably from those of the controls, there being far fewer patients with noteworthy hemorrhage among those who received ergonovine.

With reference to the route of administration, significant blood loss (over 250 c.c.) was exhibited in only 19.0 per cent of those to whom the drug was given intramuscularly post partum; in 36.2 per cent of the others (intravenous series). This tends strongly to suggest that the intramuscular route is the more efficacious. It is to be noted, however, that this subgroup received significantly more conduction anesthesia, a factor which may indeed influence the incidence of atony and blood loss.

Methylergonovine: Sixteen and eight-tenths per cent of the patients given methylergonovine tartrate post partum exhibited significant uterine atony, certainly fewer than in the control group, but not significantly different. By the intramuscular route (in 143), the drug was associated with atony 17.5 per

cent of the time; intravenously (in 24), 12.5 per cent. This illustrates a lack of real difference, in this particular respect, between these methods of administration.

Noteworthy blood loss occurred in 30.2 per cent—between 250 and 499 c.c. in 29.3 per cent and over 500 c.c. in 0.9 per cent. The remainder, 69.8 per cent, were estimated to have lost under 250 c.c. at delivery. No over-all differences were noted between intramuscular and intravenous administrations. Average blood loss was 203 ± 7 c.c., significantly less than that of the control group. This perhaps illustrated that the drug is effective in curtailing hemorrhage, both in frequency (0.9 per cent incidence) and in actual amount lost.

Dihydroergotamine: Atony characterized 23.0 per cent of the patients who received dihydroergotamine. Fifty-one per cent were felt to lose significant quantities of blood at delivery: 43.0 per cent 250 to 499 c.c. and 8.0 per cent 500 c.c. and over. Only 49.0 per cent lost less than 250 c.c. Mean over-all estimated blood loss was 255 ± 14 c.c., a large figure whose difference from that of the control group is of borderline significance. Nevertheless, the clinical impression that the use of the drug is of little or no merit as a uterotonic agent in preventing atony and combating hemorrhage is upheld.^{15, 17, 19}

This confirms the pharmacological action ascribed to hydrogenated preparations of ergot derivatives, namely, that they are biologically opposite in action to the parent substance, and may indeed block the action of the latter.^{6, 7, 14} This blocking action was implicated on the several occasions when the response expected from other oxytocics used subsequently, in particular oxytocin, was not immediately forthcoming. The method described by Leff¹⁶ notwithstanding, therefore, the use of dihydroergotamine, with or without oxytocin, as a postpartum oxytocic cannot be condoned. It is possible that its relaxing qualities can be put to effective use in other circumstances, but that is not the concern here.

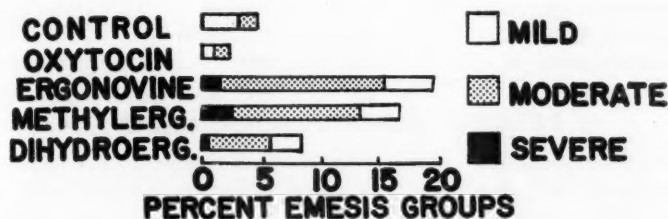


Fig. 3.—Frequency of postdelivery nausea and vomiting following the several drugs studied.

Nausea and Vomiting.—

Evaluation of the side actions of the drugs in question began with the determination of "normal" frequency of occurrence of nausea and vomiting post partum. An over-all incidence (Fig. 3) in the control group of 4.5 per cent was found, made up of 1.7 per cent mild (retching only), 2.8 per cent moderate (nausea and one or two episodes of vomiting), and none severe (intractable nausea and vomiting).

Comparable incidences were noted in the oxytocin group: 0.9 per cent mild and 1.4 per cent moderate, over-all 2.3 per cent.

In the ergonovine group, nausea and vomiting occurred in 19.5 per cent, a significant frequency. This was composed of 4.3 per cent mild, 13.3 per cent moderate, and 1.9 per cent severe. Breakdown by route of administration showed impressively more frequent and more severe nausea and vomiting following intravenous injection, significant (other than mild) emesis occurring in 19.5 per cent as against 14.4 per cent after intravenous and intramuscular administration, respectively.

The methylergonovine group, likewise, yielded significant numbers of patients with nausea and vomiting post partum, a total of 16.8 per cent, 3.6 per cent mild, 10.8 per cent moderate, and 2.4 per cent severe. There was a considerable difference noted between the intravenous and intramuscular routes, significant nausea and vomiting occurring in 16.7 per cent and 12.6 per cent, respectively.

Following dihydroergotamine, 8.0 per cent nausea and vomiting was found, 2.4 per cent mild, 4.8 per cent moderate, and 0.8 per cent severe.

These data unquestionably indicate that nausea and vomiting occur as significant side effects^{3, 4, 5, 21} following the use of ergonovine and methylergonovine. There being no other significant variable factor, the oxytocic is implicated as the offending agent.

Pressor Effects.—

In order to evaluate critically the pressor action of the drugs under investigation, blood pressure observations were obtained at 5 minute intervals for one hour post partum. In addition, available blood pressure determinations taken at any time prior to delivery (before pregnancy, during pregnancy, and during labor) were recorded for purposes of comparison. Systolic pressures over 140 mm. Hg and diastolic pressures over 90 mm. Hg were considered abnormal. A postpartum rise of 15 mm. Hg systolic and/or 10 mm. Hg diastolic above the highest previously recorded pressure was taken as being a "mild" elevation, provided that it was at or above the ascribed limits of normal, i.e., 140/90. Readings 25 and/or 20 mm. Hg, respectively, above the previous high were considered "moderate" elevations; and above that "severe."

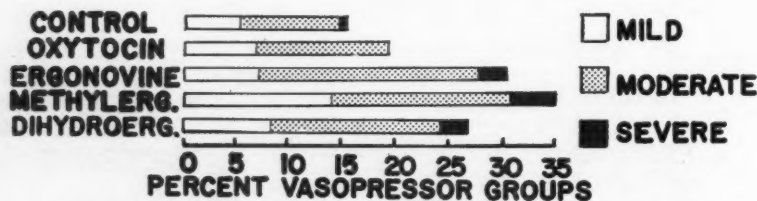


Fig. 4.—Vasopressor responses by degree (see text) as related to the administration of oxytocic principles.

Control: In the control group, 48 patients were found to have had pre-delivery abnormal pressure recordings by the above definitions, on the basis of hypertensive disease and/or pre-eclampsia. Post partum, 56.3 per cent of these were unchanged and 31.2 per cent improved. Six, or 12.5 per cent, became worse, exhibiting moderate elevations above their previous levels. There were no severe changes seen. In addition, 21 others, previously normotensive, exhibited elevations, 9 mild, 11 moderate, and 1 severe.

In all (Fig. 4) there were noteworthy postpartum pressure elevations in 15.3 per cent, 10.2 per cent of them significant (other than mild), 0.6 per cent severe. These data served as base line values for subsequent comparisons.

Oxytocin: Among 61 pre-eclamptic-hypertensive individuals in the oxytocin group, pressure levels after delivery were unchanged in 50.8 per cent, lower in 41.0 per cent, but increased in 8.2 per cent (5 patients). Of the normotensive individuals in the group, 35 demonstrated puerperal hypertension, 15 mild and 20 moderate. There were, then, 18.7 per cent pressure elevations, 11.7 per cent of them significant, none severe. These data differed in no way from those of the control group.

Ergonovine: The group which received ergonovine maleate contained 54 patients with previous blood pressure elevations. Among these, 50.0 per cent remained the same post partum, 22.2 per cent improved, and 27.8 per cent became worse. Of the latter 15 patients, 3 had severe elevations. Forty-nine others, previously normotensive, demonstrated puerperal hypertension, 15 mild, 33 moderate, and 1 severe. Over-all, 30.5 per cent elevations were noted, 23.3 per cent significant, 1.9 per cent severe. A considerable deviation from the control group was thereby found, indicating that the use of ergonovine is associated in a significant number of instances with pressor action.¹⁰

Methylergonovine: Of 43 hypertensive-pre-eclamptic patients who received methylergonovine post partum, 55.8 per cent remained unchanged and 16.3 per cent improved. There were 27.9 per cent of these, however, whose pressure elevations became more marked. Two of the latter 10 elevations were severe. Forty-six normotensive individuals also exhibited postdelivery elevations, 23 mild, 19 moderate, and 4 severe.

There were in all 34.7 per cent pressor responses, 20.9 per cent significant, 3.6 per cent severe. These data paralleled those of the ergonovine series, and similarly indicated the pressor reaction probably due to the ergot derivative used. Inasmuch as the values in this group were of the same order as those in the ergonovine group, one may assume the response elicited to be the same, other experimental evidence^{5, 11, 13, 20} to the contrary. The methylated molecule then may be said to have pressor action no different from that of ergonovine itself.

Dihydroergotamine: Thirty-five individuals had blood pressure elevations before delivery. These elevations remained unchanged after dihydroergotamine in 62.8 per cent, improved in 14.3 per cent, and became worse in 22.9 per cent. The latter 8 elevations were moderate in 7, severe in 1. Twenty-six others, normotensive before delivery, were found to have elevations of blood pressure post partum, 10 mild, 13 moderate, and 3 severe. A total of 27.0 per cent elevations were noted in all, 19.1 per cent significant, 3.2 per cent severe. These values are significantly different from the control data, but are not so impressive as those of the ergonovine and methylergonovine series.

Other Side Effects.—

The less impressive side actions variously attributed^{1, 8, 22} to the drugs under scrutiny were noted with such rarity, despite diligent search, as to interdict statistical evaluation. Tachycardia and bradycardia occurred in nearly equal frequencies, albeit rarely, in all groups including the control. No specific central nervous system manifestations were noted. Except for emesis and nausea and headache in conjunction with blood pressure elevations, patients volunteered no complaints even remotely attributable to the drugs used.

Factors Influencing Atony and Hemorrhage.—

Duration of labor: Comparison of the outcome with regard to postpartum atony and hemorrhage in patients whose labors were prolonged, of average duration, or precipitate in the several groups allowed for evaluation of the effect of the duration of labor upon puerperal uterine tonicity and hemostasis. Over-all, no real distinction was detected, 14.5, 15.2, and 10.6 per cent atony being found after prolonged, average, and precipitate labors, respectively. Blood loss aggregates were likewise not remarkable. Similar findings were noted in the control, oxytocin, ergonovine, and methylergonovine groups.

The dihydroergotamine group presented the sole exception. Contrasted with 17.2 per cent atony among patients who had had labors of average duration was 33.3 per cent atony after prolonged labors, and none after precipitate labors. Similarly, 13.3 per cent exhibited postpartum hemorrhage (500

c.c. and over) after prolonged labors, as against 5.4 and 9.1 per cent after average and short labors, respectively. If the prolonged labors in this group had been associated with diminished sympathetic stimulative activity, further blocking of sympathetic potential by a sympathicolytic agent such as dihydroergotamine^{6, 7, 14} might indeed induce relaxation. This theoretical postulate readily explains the above data and supports the pharmacodynamic action ascribed to the hydrogenated alkaloids,^{15, 17, 19} but does not concur in attributing inertia to hypertonicity,^{12, 18} a feature not universally accepted.²

Prolongation of the third stage: The incidence of postpartum atony and hemorrhage in patients with a prolonged third stage was 16.0 per cent, compared with an over-all 15.4 per cent, indicating the lack of resultant ill effects from atony in the third stage. Group data paralleled this throughout in regard to both atony and hemorrhage.

Sedation in labor: Contrasting subgroups in each series according to the sedative-analgesic effect during labor, one is able to study the influence of sedation on the production of postpartum atony and hemorrhage. Total series data of 13.0, 16.7, and 12.2 per cent incidences of atony for groups with light, moderate, and heavy sedation, respectively, indicated the absence of a mutual interrelationship. Blood loss data were also unremarkable.

The individual groups were similarly composed, except for those who received dihydroergotamine. Fifty per cent of those heavily sedated in the latter group had significant uterine atony post partum, as opposed to 17.4 per cent for average, and 13.3 per cent for light medication groups. Hemorrhage occurred in 25.0 per cent of heavily sedated patients, but in only 6.5 per cent of the moderately and 3.3 per cent of the lightly sedated, respectively. This, too, lends support to the contention stated above that a sympathicolytic drug will effectively relax myometrium already under the influence of diminished sympathetic stimulation. The latter may occur as a result of excessive sedation.

Type of anesthesia: General inhalation anesthetic agents were found to be more commonly associated with atony and hemorrhage than were conduction-type anesthetics, significant postpartum uterine relaxation occurring in 17.8 and 9.8 per cent, respectively, in the entire series, and hemorrhage in 3.0 and 1.4 per cent. This phenomenon was clearly mirrored in each of the groups without exception.

As has been noted earlier, the fortuitous weighting of the oxytocin group by excessive numbers of patients who received conduction anesthesia may have been a determining factor in producing the relative infrequency of atony. The remainder of the groups, however, were of consistently homogeneous composition, and accordingly this factor could not be implicated to account for the differences encountered.

Factors Influencing Pressor Response.—

Investigation attempting to uncover extrinsic factors possibly responsible for puerperal blood pressure elevations was undertaken. Nearly equal frequencies of pressor activity were determined in the several sedation and duration of labor groups. Significant differences, however, were discerned in the frequency of pressor responses elicited following conduction and general anesthesia, namely, 17.3 and 27.2 per cent, respectively. Parallel changes were found in each of the groups.

Conclusions and Summary

Comparative evaluation of the oxytocic drugs in current use has yielded information with regard to relative efficacy post partum, as well as the respective incidences and degrees of severity of various ill effects.

It appears, from the data compiled, that oxytocin, ergonovine, and methyl-ergonovine were all equally effective as uterotonic agents in current clinical usage for purposes of combating postdelivery atony and preventing or controlling hemorrhage. That proper management of the fourth stage of labor did not require routine use of an oxytocic agent was illustrated in the control group of patients, 78 per cent of whom did quite well without medication.

Dihydroergotamine stood alone in clinical ineffectiveness, giving evidence of actually inducing relaxation of the uterus, thereby confirming previously demonstrated experimental material¹⁹ purporting the hydrogenated alkaloids to be biologically antagonistic to their naturally occurring counterparts.

Oxytocin was found to be remarkably free of significant side effects, a feature very much in its favor from a clinical point of view. Both ergonovine and methylergonovine were shown to possess significant emetic and vasopressor properties, these responses occurring in approximately equal numbers and with comparable intensity.

In so far as practical clinical management is concerned, therefore, it may be concluded that the large majority of parturients require no oxytocic drug to aid the uterus to contract post partum. In cases where atony occurs or may be anticipated, the administration of a uterotonic agent may be of considerable value. Among the effective drugs currently available, only the purified oxytocic principle of the pituitary gland, oxytocin, has been found to be almost devoid of untoward side actions. At the same time, it is apparently equal in effect to ergot preparations when utilized post partum. Oxytocin, therefore, is recommended for routine prophylactic or therapeutic use as a fourth-stage oxytocic agent.

I should like to express my gratitude to and acknowledge the cooperation of the resident and nursing staffs of the Sloane Hospital for Women without whose aid this study would not have been feasible.

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THE POSTMATURE BABY

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A STUDY has been made of 4,106 infants delivered by primiparous women on the service of the Chicago Maternity Center in the ten-year period 1944 through 1953. Postmaturity is defined in terms of gestational age as calculated from the first day of the last menstrual period. A baby is postmature if the gestational age is 43 weeks or over. Firstborn babies were selected for study because the menstrual history of the primiparous woman was less erratic than that of the multiparous one. In the latter, frequent pregnancies gave rise to irregularities in the cycle. The population was divided into white and Negro groups. The incidence of postmaturity was ascertained in each. The effect of prolonged gestation on infant mortality and the size of the fetus was studied. The degree of confidence which could be placed in gestational age as a method for determining fetal development was tested. Chi square was used on the data where indicated.*

Nesbit¹ has recently written a comprehensive and excellent review of the literature in "Prolongation of Pregnancy." His bibliography is complete and it is doubtful if anyone can improve upon his presentation. The discussion which follows reflects the highlights of his paper to which are added references to the work of Clifford and Smith.

An amazing amount of interest has been shown recently in the subject of the postmature baby. Until five or six years ago little appeared in the literature in this country on prolonged gestation. Many physicians doubted the validity of postmaturity and others considered that if it did exist it was of no clinical importance.

The possibility of postmaturity is now being recognized. Most authors consider a baby postmature if the gestational age is 43 weeks or over. The incidence quoted is from 3 to 8 per cent.²⁻⁶

Some define postmaturity in terms of size in addition to gestational age. By this criterion the gestational age is 43 weeks or over, the baby weighs 4,000 grams or more and measures 53 to 56 cm. The baby is thought to increase progressively in size during the postmature period. Wrigley⁷ believed this to be true. Karn and Penrose⁸ in a study of 14,000 infants found a gradual increase in weight for two weeks beyond term, after which the weight is constant or slightly lower.

Bone growth as determined by the time of the appearance of various ossification centers has also been used to define postmaturity.^{9, 10} Tables are available which display the usual time of appearance of these centers.¹¹ Roentgenography is used to visualize the fetal skeleton. The ossification center in the distal end of the epiphysis of the femur can frequently be seen before

*Chi square is a formula which ascertains the probability of chance occurrence of comparative statistical data.

birth. Unfortunately, there is too great a variation in the time of its appearance (35 to 44 weeks)¹¹ to make its presence or absence of value in the diagnosis of gestational age.

Smith¹² and Clifford¹³ found that the postmature baby is relatively light in weight compared to its length. They noted the following characteristics: there is little vernix; the skin is loose, wrinkled, exfoliating, and meconium stained, and the nails are long. They found that the perinatal mortality rate is higher than in the mature baby. The postulation is made that the condition of the infant is due to changes which occur in the placenta due to aging. These prevent an adequate transfer of oxygen and metabolites from the mother to the baby. The baby consequently suffers from anoxia and malnutrition. Depending upon the degree of impairment, death may occur before, during, or after labor. In other cases the child survives. At times the clinical course in the postpartum period is similar to that displayed in hyaline membrane disease.

The vagaries of placental function and morphology have not been determined in prolonged gestation.¹ Masters and Clayton¹⁴ concluded that postmature placentas show no more degeneration than mature placentas. Hill¹⁵ found that 40 per cent of postmature placentas showed evidence of infarction and calcification. McKiddie¹⁶ postulated that microscopy and chemical analysis of the placenta might not necessarily show changes indicative of a hampered physiology.

Opinions differ as to the significance of prolonged gestation in regard to survival of the infant. While Hill¹⁵ concluded that "postmaturity does not affect adversely the mother, her labor or her infant," Clifford¹³ of the Boston Lying-in Hospital stated that "in the primiparous woman postmaturity is second only to prematurity as a cause of infant death." Walker,¹⁷ an English observer, found in 11,051 patients of all parities, that the stillbirth rate was three times as high at 43 weeks' gestation and over as at 40 weeks. Clayton¹⁸ and Rathbun¹⁹ found no increase in the stillbirth rate without evident cause. They found that the higher mortality rate is due to difficult labor and delivery. No infant died as a direct result of the prolongation of pregnancy. Wrigley,⁷ Calkins,²⁰ Eastman,²¹ and Daichman and Gold⁶ felt that there is no problem with postmaturity. Daichman⁶ stated that the case of postmaturity should receive the same management as that of the mature infant. He believes the term "postmaturity" dangerous because it leads to unnecessary interference, with bad results. The suggestion is made that the term "post date labor" be substituted.

The question arises as to what are the indications for the termination of pregnancy in cases of prolonged gestation. Until recently the attitude of obstetricians was governed by the individual case, based primarily on fetal size in relation to pelvic size. Induction was carried out if the fetus was becoming excessive in size and mild disproportion seemed likely. In case of insurmountable disproportion cesarean section was done. During the past fifteen years elective induction of labor for postmaturity has been increasingly used in many clinics in England. Impetus has been given to this practice recently through the cord blood studies of Walker.¹⁷ He has found that there is a progressive diminution in oxygen content and saturation as pregnancy advances beyond term. Rooth and Sjöstedt²² are unable to substantiate Walker's findings. They conclude that hypoxia does not explain the higher mortality in infants delivered by mothers with a gestational time longer than 294 days. Even Smith¹² and Clifford,¹³ who believe that prolonged gestation has a direct bearing on infant mortality, are guarded in recommending the termination of pregnancy by induction or cesarean section.

Incidence

Of the 4,106 children, 832 were white and 3,274 were Negro. In 32 of the white and in 45 of the Negro mothers the date of the last menstrual period was not known or the cycle recurred irregularly. The babies of these mothers were deducted from each group, respectively. Table I shows the incidence of postmaturity. The incidence in the white group is 9 per cent; in the Negro, 6 per cent. The higher incidence in the white group probably has no significance. The information given from maternal recollection regarding the date of the last menstrual period was less reliable in the white patient.*

TABLE I. THE INCIDENCE OF POSTMATURITY IN THE FIRSTBORN BABIES DELIVERED AT THE CHICAGO MATERNITY CENTER, 1944-1954

RACE	TOTAL NO.	LAST MENSTRUAL PERIOD		POSTMATURE BABIES	
		?	KNOWN	NO.	%
White	832	32	800	75	9.3
Negro	3,274	45	3,229	192	5.9
Total	4,106	77	4,029	267	6.6

Perinatal Infant Mortality

The perinatal mortality rate was determined for white and Negro mature and postmature infants. A mature baby weighs 2,500 grams or over. The perinatal deaths include intrauterine deaths and neonatal deaths. Intrauterine death occurs either ante partum or during labor and the baby is born dead. Neonatal death occurs during the first month of life. The number of mature babies was calculated by subtracting from the total the number of prematures, postmatures, and the babies born of mothers whose last menstrual period was unknown or whose cycle recurred irregularly. A premature baby weighs less than 2,500 grams.

Two infant deaths were deducted from the Negro postmature group. In one case the baby died during the forty-second week of pregnancy and was delivered one week later. This death was assigned to the mature group. In the second instance the infant was a twin, the second baby. The first twin lived. The gestational age was 48 weeks. The baby weighed 2,200 grams. The pathologist stated that the baby appeared to be a premature of about 36 weeks' gestation. The mother gave a history of markedly irregular menstrual periods. This death was not assigned to either group.

Table II shows the perinatal mortality of the white and Negro mature and postmature babies. The percentage of loss in the white group is 1.4, compared with 1.3 in the postmature group. The percentage of Negro mature babies lost is 2.3, compared with 3.1 in the postmature group. There is no statistically significant difference in the perinatal mortality rates of either the white or the Negro mature and postmature groups ($P = .17$).

A study was made of the perinatal records of the 7 babies, one white and 6 Negro, lost in the postmature group. In 2 patients pregnancy was diagnosed in the first trimester. The gestational ages varied from 43 to 47 weeks. Two of the mothers had syphilis and were treated during pregnancy. Five had toxemia. The blood pressure ranged from 150/110 in one patient to 180/140 in another. Three of the patients had albuminuria. Five of the 7 were delivered after prolonged labor. The labors lasted from 27 to 71 hours. In 2,

*The date of the last menstrual period is recorded twice on each perinatal record, once at the first visit on the prenatal record and again at the time of delivery on the labor record. A discrepancy in the two recordings occurred more often in the white group. Where a discrepancy did occur the most plausible date was chosen for the calculation of gestational age.

the babies died early in labor and were delivered by craniotomy. Two were persistent posterior presentations, delivered after manual rotation by forceps. There were 3 breech deliveries. Four of the babies were large, weighing from 3,700 to 4,300 grams.

There were no antepartum intrauterine deaths; 4 died intra partum and 3 died neonatally. Autopsies were performed on 6 of the 7 babies. One breech baby died from interstitial and periarterial emphysema secondary to resuscitation by tracheal catheter. A second breech baby died neonatally from pneumonia probably secondary to intrauterine asphyxia. The autopsies were non-contributory as to the cause of death in the intrapartum group.

It will be seen that each death could have been due either to difficult labor and delivery, or toxemia, or infection. We agree with Nesbit¹ who states, "It is fallacious to attribute total fetal mortality to any single factor such as postmaturity without correcting for associated clinical and pathological conditions." Only one of these deaths might possibly have been due to prolonged gestation. This will be discussed below.

TABLE II. THE PERINATAL MORTALITY RATE OF WHITE AND NEGRO MATURE AND POSTMATURE FIRSTBORN BABIES AT THE CHICAGO MATERNITY CENTER, 1944-1954

RACE AND GESTATIONAL AGE	NO. BABIES	DEATHS	
		NO.	%
<i>White.</i> —			
Mature	634	9	1.4
Postmature	75	1	1.3
<i>Negro.</i> —			
Mature	2,611	61	2.3
Postmature	192	6	3.1

Unusual Ratio of Weight to Length Associated With Placental Pathology and Intrauterine Death

The theory has been advanced that in prolonged gestation changes occur in the placenta due to aging which cause anoxia and malnutrition, which lead to intrauterine or neonatal death. Two cases are presented which possibly but not conclusively support this theory.

One was that of a premature baby, classified as such by weight and gestational age. The mother's prenatal course was not remarkable. This baby was delivered spontaneously after a thirty-one-hour labor at the thirty-seventh week of gestation. It weighed 2,200 grams and measured 49 cm. Intrauterine death occurred two hours prior to birth. The body was meconium stained and poorly nourished. No cause of death was found at autopsy. Secondary centers of ossification were present and the pathologist remarked that the tissues examined could not have been those of a premature baby. The placenta was very small and thin. One-fourth of the tissue was replaced by infarcts. Another large part was nonfunctional because of a clot in one of the larger vessels.

The second case was that of a postmature baby of 47 weeks' gestation. The mother had a positive Wassermann test and received what was thought to be adequate antisyphilis treatment during the seventh month of pregnancy. This baby was born in breech presentation and died late in the second stage of labor which lasted two and a half hours. The delivery was spontaneous. The baby weighed 2,500 grams and was 51 cm. long. The attendant noted that the baby was emaciated and meconium stained. At autopsy no evidence of syphilis was found in either the baby or the placenta. Petechiae characteristic of anoxia were found in the lungs and heart. About half of the substance

of the placenta was replaced by granular infarcts. Microscopic examination disclosed that most of the villi were degenerated and buried in fibroid material.

The Effect of Postmaturity on Infant Weight

The effect of postmaturity on infant weight was studied. The birth weights of the babies in the white and Negro mature and postmature groups were compared. The babies were all born at home and weighed on spring scales. Whatever error which may have occurred in weight is for the purposes of this study considered constant. The babies were divided into four groups by weight: 2,500 to 2,700 grams, 2,700 to 3,200 grams, 3,200 to 3,700 grams and 3,700 grams and over. The data are shown in Table III. The largest number of mature white babies fell into the 3,200 gram division, while the largest number of mature Negro babies weighed 500 grams less and fell into the 2,700 gram group. The percentage of large babies was higher and the percentage of small babies was less in both the white and the Negro postmature groups. This is statistically significant; P is less than 0.001.

TABLE III. THE BIRTH WEIGHTS OF WHITE AND NEGRO MATURE AND POSTMATURE FIRSTBORN INFANTS AT THE CHICAGO MATERNITY CENTER, 1944-1954 ($P < 0.001$)

	WEIGHT								TOTAL	
	2,500 GRAMS		2,700 GRAMS		3,200 GRAMS		3,700 GRAMS +			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
<i>White.—</i>										
Mature	46	7.2	184	29	244	38.5	160	25.3	634	100
Postmature	2	2.6	17	22	28	39	28	36.4	75	100
<i>Negro.—</i>										
Mature	223	8.5	992	38	887	34	509	19.5	2,611	100
Postmature	5	2.4	60	31	82	43	45	23.6	192	100

The problem was approached from a different angle. The incidence of postmaturity of large and of average-sized babies was ascertained and compared. The data presented are taken from a study in progress on "The Larger Babies Born on the Service of the Chicago Maternity Center." This includes all babies that weighed 4,500 grams and over born during the twenty-year period, 1934-1954. During this time there were 55,246 deliveries. Among these were 1,507 large babies. In 45 the date of the last menstrual period was not known or it recurred irregularly. These were deducted, leaving 1,462. The gestational age was determined for each child and compared with the gestational ages of 1,005 average-sized babies whose mothers had last menstrual periods of known date and regular cycles. The latter group was made up of samplings chosen at random. Every fifty-third chart in the series was pulled and the date of delivery noted. The chart of the 3,200 gram baby born nearest to this date was studied.

Table IV gives the gestational ages of the large and average-sized babies born to mothers of all parities and races (white, Negro, and one Chinese).

TABLE IV. GESTATIONAL AGE OF LARGE (4,500 GRAM AND OVER) BABIES AND AVERAGE-SIZED (3,200 GRAM) BABIES BORN OF MOTHERS OF ALL RACES AND PARITIES ON THE SERVICE OF THE CHICAGO MATERNITY CENTER, 1934-1954 ($P < 0.0001$).

WEIGHT	GESTATIONAL AGE				TOTAL	
	LESS THAN 43 WEEKS		43 WEEKS AND OVER			
	NO.	%	NO.	%	NO.	%
4,500 grams +	1,237	85	225	15	1,462	100
3,200 grams*	942	93.7	63	6.3	1,005	100

*Sampling.

Table V shows the gestational ages of large and average-sized firstborn Negro and white babies.

TABLE V. THE INCIDENCE OF VARIOUS GESTATIONAL AGES OF THE LARGE AND THE AVERAGE-SIZED FIRSTBORN BABIES, CHICAGO MATERNITY CENTER, 1934-1954 ($P = 0.11$)

WEIGHT	GESTATIONAL AGE				TOTAL	
	LESS THAN 43 WEEKS		43 WEEKS AND OVER			
	NO.	%	NO.	%	NO.	%
4,500 grams +	55	86	9	14	64	100
3,200 grams*	162	93	12	7	174	100

*Sampling.

The incidence of postmaturity for large babies, 4,500 grams and over, is 15 per cent, as compared with 6 per cent for average-sized babies. Statistically this is highly significant. More large babies are postmature than average-sized babies. The infant mortality rate of the large babies was three times as great as that of the average-sized babies. None of these babies died as a direct result of postmaturity. Over 60 per cent were lost because of shoulder dystocia. In a hospital where anesthesia is readily available, this figure undoubtedly would have been less.

The degree of confidence which can be placed in gestational age, as calculated from the first day of the last menstrual period, as a method of determining fetal development was tested. The degree of development after birth is usually determined by weight. A premature baby weighs less than 2,500 grams. Such a baby usually has a gestational age of less than 38 weeks. The percentage of white premature babies with a gestational age of 38 weeks or over was determined and the percentage of white mature babies with a gestational age of less than 38 weeks was determined. There were 91 premature infants among the 832 white firstborn infants and 30 of these, or 27 per cent, had a gestational age of 38 weeks or more. Of the 632 white mature infants, 176, or 28 per cent, had a gestational age of less than 38 weeks. We conclude that gestational age is a very crude method of ascertaining fetal development.

Summary

Of the 4,106 firstborn infants, 832 were white and 3,274 Negro. The incidence of postmaturity in the white group was 9 per cent and in the Negro group, 6 per cent.

The perinatal mortality rate in the mature white group was 1.4 per cent; in the postmature white group, 1.3 per cent.

The perinatal mortality rate in the mature Negro group was 2.3 per cent; in the postmature Negro group, 3.1 per cent.

Two small babies died of malnutrition and anoxia during labor. The placenta of each showed changes which might have been attributed to aging.

There were 5 per cent fewer small babies (2,500 grams) in the postmature white group than in the mature white group.

There were 6 per cent fewer small babies in the postmature Negro group than in the mature Negro group.

In the mature white group the largest number of babies fell into the 3,200 gram division. This was also the largest division in the postmature white group. There was a 1 per cent increase in 3,200 gram babies and a 10 per cent increase in babies weighing 3,700 grams and over in the postmature white group over the mature white group.

In the mature Negro group the largest number of babies fell into the 2,700 gram division, while in the postmature Negro group the largest number fell into the 3,200 gram division. There was a 13 per cent increase in 3,200 gram babies and a 3 per cent increase in babies who weighed 3,700 grams and over in the postmature Negro group over the mature Negro group.

From a study of "The Larger Babies Born at the Chicago Maternity Center," the incidence of postmaturity for large babies (4,500 grams and over) born of mothers of all races and parities is 7 per cent greater than for average-sized babies (3,200 grams). The same increase in the incidence of postmaturity is found for large firstborn babies over average-sized firstborn children.

Twenty-seven per cent of white premature babies classified by weight fall into the mature group when classified by gestational age.

Twenty-eight per cent of mature babies classified by weight fall into the premature group when classified by gestational age.

Conclusions

There is a high degree of error in determining fetal development by gestational age and any conclusion drawn from a study such as this must be evaluated accordingly.

The incidence of postmaturity is 6.6 per cent (total population).

There is no statistically significant difference in the perinatal mortality rates of mature and postmature infants.

Prolonged gestation is rarely accompanied by placental changes which lead to malnutrition, anoxia, and death.

Postmature babies tend to be larger than mature babies.

The incidence of postmaturity is 7 per cent higher in large babies than in average-sized babies.

The case of a postmature infant requires no different management than that of the mature infant.

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PRECIPITATE LABOR

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IT IS a common belief that tumultuous and brief labors are not desirable and often result in an increased incidence of damage to both the mother and her baby.^{1, 2, 3} A labor of three hours or less, which includes the summation of the first, second, and third stages, is recognized as precipitous and is set apart as being unusually brief from the usual length of parturition. Precipitate labor is to be differentiated from precipitate delivery which is an unexpected and rapid termination of labor. This paper shows that both mother and baby react favorably to precipitate labor, which in some respects is more desirable than parturition of the average length.

Precipitate labor reportedly^{1, 4, 5} occurs from 6 to 14 times in every 100 labors. In this analysis, taking the labors for the past six years at the State University of Iowa Hospitals, there is an incidence of 10.2 per cent, or 731 precipitate labors in a total of 7,179 births. Table I indicates the constancy of incidence and the annual number of births.

TABLE I. INCIDENCE OF PRECIPITATE LABORS DURING A SIX-YEAR PERIOD

YEAR	NO. OF DELIVERIES	NO. OF PRECIPITATE LABORS	% INCIDENCE
1950	1,173	134	11.4
1951	1,145	112	9.8
1952	1,017	105	10.3
1953	1,158	117	10.1
1954	1,378	143	10.4
1955	1,308	120	9.2
Total	7,179	731	10.2

Certain factors seem to enhance the likelihood of a patient's having a rapid labor. Ninety-five per cent of such labors occurred in parous women. However, the parity need not be great, for about half of the patients had had only either one or two previous deliveries. It seems to be uncommon for a primigravida to have a labor of this type, since there were only 39 in this series, an incidence of 5 per cent.

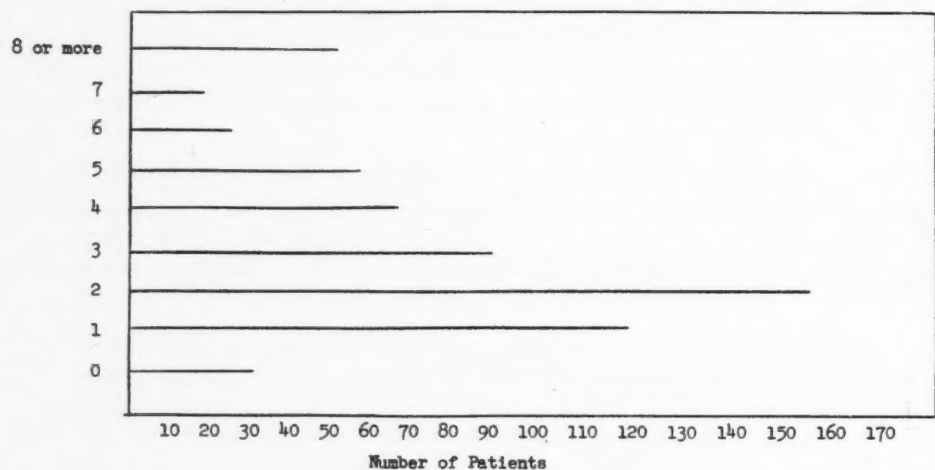
Another predisposing factor was the patient's previous experience with precipitate labor. Four out of 10 patients in the series gave a history of a past labor of three hours or less (Fig. 1).

As far as body weight at the time of delivery is concerned, there is no characteristic habitus, but there is some statistical significance to the stature of the patients, since over one-half were between 5 feet, 2 inches, and 5 feet, 4 inches in height.

Perhaps another factor contributing to rapid labor was that the baby was delivered as an occiput anterior in 96 per cent of the cases. There were only 10 babies delivered in an occiput posterior position, which, according to Plass,⁶

slightly lengthens labor. Our finding of only 1 per cent persistent occiput posteriors would fit in with this generally accepted idea, that this position usually requires a longer labor than the average. There were 19 sets of twins in the series of precipitate labors, an incidence twice that which is usually reported for twin pregnancy. According to DeLee and Greenhill,⁷ the length of labor in twin pregnancy is longer than the average. Our experience, however, indicates that twins tend to have a precipitate labor more often than single pregnancies. In this six-year period there were 102 sets of twins in all labors with an incidence of precipitate labor of 1 out of 5, or 20 per cent.

As one might expect, the incidence of pelvic contraction was considerably less than average. Ninety-six per cent of the patients had normal measurements while 2 per cent had a funnel pelvis and 0.5 per cent a simple flat type. There were no generally contracted pelves in the group. Since the evaluation of the midpelvis depends largely upon routine x-ray pelvimetry, no definite estimation could be made of the incidence of this type of contraction.



DISTRIBUTION OF PRECIPITATE LABORS ACCORDING TO PARITY

Fig. 1.

Among some obstetricians there is a feeling that patients with severe cardiac disease and toxemia often have rapid labors. With some interest, a tabulation was made of the number of patients who had heart disease, toxemia, antepartum bleeding, and some of the other major complications of pregnancy. From this study it appears that the patients who had precipitate labors had fewer antepartum complications than the average for the entire group. Saying this in another way, the patients with precipitate labor were as obstetrically healthy as the average, and there could be no bias introduced because of those who were severely ill. A comparison of the incidence of complications in the precipitate group with the accepted average is shown in Table II.

At the University of Iowa Hospitals about one out of 5 labors is induced either by medical means with fractional amounts of Pitocin given intramuscularly or intravenously, or by rupture of the membranes, or a combination of these methods (Table III). In this series of 731 precipitate labors, there is a definite relationship between the rapid course of labor and the induction of labor, but one's enthusiasm for induction should be tempered by the obvious inherent dangers involved.

TABLE II. COMPLICATIONS OF PREGNANCY IN PRECIPITATE LABOR GROUP

COMPLICATION OF PREGNANCY	% INCIDENCE IN PRECIPITATE GROUP	ACCEPTED AVERAGE INCIDENCE (%)
Toxemia	8.1	6 to 7.0
Diabetes mellitus	0.7	< 0.5
Placenta previa	0.3	0.5
Premature separation of placenta	0.7	0.4 to 1.3
Unexplained antepartum bleeding	1.0	0.2
Nephritis	0.3	1 to 2.0

TABLE III. RELATIONSHIP OF ONSET OF LABOR TO PRECIPITATE LABOR

METHOD OF ONSET OF LABOR	NUMBER HAVING PRECIPITATE LABOR	INCIDENCE OF PRECIPITATE LABOR
Artificial induction of labor	182	One out of 7
Normal spontaneous onset	544	One out of 11

The time required for each of the three stages of precipitate labor is proportionally the same as that in each of the three stages of the accepted normal duration of labor (3 to 30 hours). There is little significance to a breakdown as far as the first and second stages are concerned, but the decreased time for the third stage contributes to a lower incidence of postpartum hemorrhage in the precipitate labor group. There is an average incidence of postpartum hemorrhage of 4 to 5 per cent in the general run of obstetrical cases. In the precipitate group, however, this figure is reduced by more than one-half. Table IV shows that the incidence of postpartum hemorrhage in normal and prolonged labor at the State University of Iowa Hospitals compares favorably with that reported from other clinics. However, when these two groups are contrasted with the precipitate labor series, there is an outstanding reduction in incidence of hemorrhage for the latter. It is generally believed that a prolonged third stage is accompanied by an extraordinarily high rate of postpartum hemorrhage. Since 84 per cent of the patients in the series had a third stage of 9 minutes or less, with only 4 patients having a prolonged third stage (30 minutes or more), one might give some weight to the relative shortening of the third stage of a precipitate labor as a cause of decreased postpartum hemorrhage. Accompanying factors which also probably influenced this reduction in hemorrhage were the 3 per cent rate of operative obstetrics, the low incidence of general anesthesia (16 per cent) for delivery, and the fact that almost all patients received intravenous ergonovine either with the birth of the anterior shoulder or shortly after delivery of the baby. The placenta was removed manually in 2 per cent of the cases. This incidence does not reflect the actual necessity for manual removal since in recent years it has been the policy to encourage elective manual removal of the placenta in order that interns and residents may become proficient in performing the procedure in a controlled situation.

TABLE IV. POSTPARTUM HEMORRHAGE IN PROLONGED, NORMAL, AND PRECIPITATE LABOR

TYPE OF LABOR	NUMBER OF LABORS	CASES OF POSTPARTUM HEMORRHAGE	INCIDENCE OF POST- PARTUM HEMOR- RHAGE (%)
Normal (3 to 30 hours)	19,070*	945	5.0
Prolonged (30 hours)	422†	32	7.6
Precipitate	731	14	1.9

*1936 to 1952.

†1926 to 1942.

The mothers reacted favorably not only by a reduction of postpartum hemorrhage but also as mirrored in the lack of complications of labor. There

were no tetanic uteri, no acute inversions of the uterus, no rupture of the uterus, or other phenomena which in the past have been thought to be related to an extremely rapid type of parturition. Indeed, 2 out of 5 patients had no laceration or need of episiotomy. The postpartum course was unusually devoid of the annoying complications that bother the newly delivered mother. There was one urinary tract infection, one breast infection, but no cases of parametritis or thrombophlebitis. There was a 10 per cent incidence of one-day fevers and a 4 per cent morbidity, both findings being average for the clinic.

Contrary to the popular belief, the babies behaved as well as, if not better than, those resulting from a labor designated as normal in duration. Even though half of the patients had sedation, only 8 per cent of their infants were regarded as mildly asphyxiated and responded quickly to simple nasopharyngeal suction by bulb, or to external stimulation. Less than 1 per cent of the infants (7 cases) were clinically severely asphyxiated, and were resuscitated with oxygen after the upper respiratory passages were cleared by bulb suction or by tracheal catheter. Including all labors of 3 hours or less which resulted in an infant of 750 grams or over, there was a perinatal mortality of 3 per cent. Of 22 fetal deaths, 13 were stillbirths, while the other 9 occurred in the early neonatal period. If a common denominator was present in the stillborn babies, it was the observation that all of the babies died prior to the onset of labor. On the other hand, 5 of the 9 neonatal deaths occurred during the first day of life. There was no common pathological stigma in the deadborn babies. Table V shows the most obvious cause of neonatal death. One should note that intracranial hemorrhage accounted for only one death. As would be expected, the incidence of prematurity in the neonatal death group was higher than the average. For the entire series there was an incidence of prematurity of 10 per cent which is approximately 50 per cent greater than the clinic average of 7 per cent.

TABLE V. NEONATAL DEATHS

FETAL WEIGHT (GRAMS)	OBLIVIOUS PATHOLOGICAL CAUSE OF DEATH
1. 3,451	Cardiac anomaly not compatible with life
2. 2,865	Hydrops fetalis
3. 1,935	Bilateral atelectasis
4. 1,530	Intracranial hemorrhage
5. 755	Severe prematurity
6. 2,347	Cardiac anomaly not compatible with life
7. 750	Severe prematurity
8. 2,680	No postmortem (mother was diabetic with hydramnios)
9. 1,500	Necrosis and rupture of terminal ileum

Comment

Until recently a precipitate course of labor has been considered by many as an obstetric complication. The reasons for thus condemning it are primarily twofold. First, there is a paucity of literature that deals in a comprehensive way with the maternal and fetal reactions to this type of parturition. Second, in some people's minds there is confusion over the precipitate course of labor, and precipitate delivery, which is often dangerous because the patient is delivered unexpectedly and usually without attendants.

The feeling that harm will result to the mother and her child from a rapid labor is not borne out by this analysis. It seems logical that a normal pelvis, an anterior vertex presentation, and multiparity are important factors

in precipitate labor, but it is more difficult for some to accept that a reduction in postpartum hemorrhage and a desirable fetal survival should also be associated with this type of labor. This paper confirms many of Karlovsky and Thoms'⁴ recent observations on precipitate labor and is consistent with Tucker and Benaron's⁸ statement that there is no significant increase in the incidence of intracranial hemorrhage with a rapid type of parturition. These latter investigators, however, are of the opinion that there is an increased number of children who show signs of brain damage later in life from this type of labor. The validity of their observations is limited by a follow-up in only 45 cases.

Considering the findings from our analysis, one can logically conclude that precipitate labor is not an obstetric complication but a relatively innocuous variation from normal. Its benignity in regard to the mother and her baby would rule against meddling with the natural course of precipitate labor by using such measures as general or spinal anesthesia or heavy sedation to retard its rapidity. On the other hand, the advantages of a rapid type of parturition are not so striking as to justify acceleration of the usual course of labor with oxytocics or rupture of the membranes.

Summary and Conclusions

1. During the past 6 years at the State University of Iowa Hospitals there have been 7,179 labors with 731 precipitate labors, or an incidence of 10.2 per cent.
2. Multiparity, previous precipitate labor, normal pelvis, and an average prenatal course favor precipitate labor.
3. An occiput anterior presentation, twin pregnancy, and a slightly increased incidence of prematurity are fetal factors associated with precipitate labor.
4. Risk to mother and baby is no greater than in the average type of labor, and, in fact, the incidence of postpartum hemorrhage is reduced by more than one-half.
5. Induction of labor predisposes to precipitate labor, but this advantage should be tempered by the inherent dangers of such a procedure.
6. The use of such measures as heavy sedation and general or spinal anesthesia to slow a precipitate labor seems unwarranted.

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RUPTURE OF THE SPLEEN IN PREGNANCY

A Review of the Subject and a Case Report

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THE frequency with which rupture of the spleen is associated with pregnancy is impossible to state. Barnett¹ in an excellent review of the subject in 1952 collected 28 cases. Since Barnett's report, 4 additional cases²⁻⁵ have been reported as of January, 1955. We are reporting an additional case, thus bringing the total to 33. Sixteen of the 33 patients died. Of the 16 fatal cases, 9 occurred prior to 1900, however.

Ruptures of the spleen are classified as traumatic and spontaneous and occur in both categories in normal and diseased spleens, if published case reports are authentic.

The anatomy of the spleen per se renders that organ susceptible to rupture. The splenic pulp is soft and of necessity highly vascular. Trauma of minimal intensity can at times result in intracapsular rupture of the splenic pulp with resulting hematoma formation. When the hematoma has reached sufficient size, the splenic capsule, which is never strong, ruptures with resulting intraperitoneal bleeding. These facts account for the period of delay between the original trauma and the onset of objective and subjective symptoms reported in numerous cases of rupture of the spleen in both the pregnant and nonpregnant state.

The case we will report is one of that type.

Diseases of the spleen that have been reported as being present in spleens which have ruptured are numerous and are as follows: malaria, typhoid fever, leukemia, portal thrombosis, Banti's syndrome, infectious mononucleosis, septic infarct of the spleen, puerperal sepsis, relapsing fever, pneumonia, typhus fever, and hemangioma of the spleen.

For anatomical description, the spleen is divided into an anterior and a posterior segment. The segments are separated by a sulcus, the so-called hilus of the spleen. The hilus is located on the inner, concave or peritoneal surface of the spleen. The splenic vessels enter into this area by way of the so-called splenic pedicle. Truex,^{6*} in a personal communication on the subject of the anatomy of the spleen, stated that the length of the splenic pedicle and the depth of the splenic sulcus were extremely variable. He further stated that an unusually short pedicle and/or a deep sulcus are not uncommon. These facts, we feel, are important because on the external, convex or diaphragmatic surface of the spleen opposite the hilus is attached the principal

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suspensory ligament of that organ to the left crux of the diaphragm, the so-called lieno splenic ligament. Therefore, a sudden change in the position of the left diaphragm, caused, for instance, by a cough, sneeze, strain, blow, etc., can and does at times result in rupture of the spleen in the region of the hilus. It is reasonable, then, to feel that a short splenic pedicle and/or an unusually deep splenic sulcus in certain individuals would render the spleen of such an individual more susceptible to rupture.

Case Report

A young woman, gravida i, para 0, at the thirty-ninth week of gestation (calculated), was admitted to the hospital because of severe epigastric pain. The patient had made routine prenatal visits since the ninth week of her pregnancy. The pregnancy had been completely normal.

Seven and three-quarter hours prior to admission to the hospital the patient had slipped and fallen, striking her back on a footstool with apparently little injury to herself. Five hours later and two and three-quarter hours prior to entering the hospital, however, the patient developed epigastric and high back pain and pain at the nape of the neck.

On admission she was complaining bitterly of epigastric pain *only*. No history of vomiting or vaginal spotting was obtained and the urine was reported as failing to show evidence of gross blood.

Physical examination was as follows: pulse 86, blood pressure 120/80. No contusions were demonstrated and no back or costovertebral tenderness was elicited. Abdominal palpation disclosed the epigastrium to be soft and nontender. The tone of the uterus was unusually high but no areas of tenderness could be elicited. The fetal heart tones were good at 140 beats per minute.

Rectal examination failed to disclose or precipitate any vaginal bleeding. The cervix was found to be 2 cm. dilated and 80 per cent effaced. The fetal head was at station minus 1. An immediate catheterized urine specimen failed to reveal gross blood.

Atypical separation of the placenta and intra-abdominal hemorrhage (rupture of the spleen) were considered. Hemoglobin and hematocrit determinations and a complete blood count were ordered.

Forty-five minutes after admission, while the report on the blood was being awaited, the patient broke out in a mild sweat. The blood pressure fell to 80/65 and the fetal heart rate to 80. The maternal pulse, however, remained below 90. Within ten minutes the blood pressure rose to 105/65 and the fetal heart rate to 130. Within minutes, thereafter, the fetal heartbeat rose to 180 and persisted between 160 and 180. No uterine contractions were demonstrated but the unusually high uterine tone persisted. There was no change in the status of the cervix. The blood report was as follows: hemoglobin 9.7 Gm., hematocrit 33, red cells 2.6 million. An immediate abdominal section under cyclopropane anesthesia was performed.

There was free intraperitoneal blood in the abdomen. The uterus showed marked hypertonicity but was otherwise normal. Exploration of the upper left abdomen revealed a large hematoma involving the anterior half of the spleen. A rapid classical cesarean section was performed and a living infant, in good condition, obtained. A few through-and-through silk sutures (Potter technique) were placed in the uterine incision, after which the gastrocolic ligament was opened and a splenectomy performed.

The hematoma involving the anterior half of the spleen was larger than that of a normal-sized spleen. There was an incomplete rupture of the splenic capsule which was leaking.

No blood was demonstrated in the intact amniotic sac. The placenta was found to be attached high on the uterine fundus and failed to show any area of separation. It was estimated that there had been between 500 and 600 c.c. of free blood in the peritoneal cavity prior to the cesarean section.

The postoperative convalescence was complicated by pulmonary atelectasis involving the lower left lobe. The atelectasis was noted within ten hours following operation and responded nicely to tracheal catheter aspiration. The patient was discharged on the eleventh postoperative day.

The biopsy report was as follows: Diagnosis, spleen. Laceration at hilus with hemorrhage.

Comment.—Had our patient not been pregnant at term, we feel a diagnosis of splenic rupture could have been made simply on the basis of history and subjective symptoms alone. The fact that no abnormalities in the cardiovascular system could be demonstrated or positive physical signs elicited did not preclude such a diagnosis. We feel that during the five-hour period between the fall and the onset of epigastric, high back, and neck pain the hematoma of the spleen was forming. Pain ensued when the hematoma became of sufficient size to produce a minimal rupture of the splenic capsule with gross peritoneal staining with blood. The attack of syncope forty-five minutes after admission, we feel, occurred when the hematoma in the process of rupturing soiled the peritoneum with a goodly quantity of blood. We can only theorize as to why the patient recovered so rapidly from her shock or why her cardiovascular system remained stable thereafter. We believe the bleeding from the spleen was sporadic. The gross appearance of the spleen tends to substantiate such reasoning in that the capsule over the hematoma was not completely disrupted at operation.

The sudden drop in fetal heart rate can be explained on the basis of circulatory failure in the mother. Why the fetal distress after the stabilization of the maternal circulation? Why the semitonic uterus? We have had no prior experience with gross intraperitoneal hemorrhage of nonobstetrical origin in a woman at the thirty-ninth week of gestation. The literature is of little help. We can, therefore, only theorize that the presence of intraperitoneal blood of a sufficient, but unknown quantity, can precipitate tonic contractions of the uterine musculature and that the uterine tetany interferes with placental function on a purely mechanical basis with resulting fetal anoxia.

Barnett,¹ however, emphasized several diagnostic points in discussing the differential diagnosis between rupture of the spleen and concealed uterine bleeding that our case failed to demonstrate. He emphasized epigastric pain and rigidity as being very suggestive of intraperitoneal blood secondary to rupture of the spleen.

Although our patient complained bitterly of epigastric pain, the entire abdominal wall, including the epigastrium, was nontender and nonrigid. It appears that tenderness and rigidity of the abdominal wall would depend upon the quantity of free blood in the peritoneal cavity. In our case there was a relatively small amount, 500 to 600 c.c. Barnett further stated, as important findings in the differential diagnosis between ruptures of the spleen and concealed uterine bleeding, the fact that the uterus in rupture of the spleen does not become spastic, fetal parts can be palpated, and the fetal heartbeat is present and of relatively normal rate.

In our case, uterine tetany of moderate degree and later changes in the fetal heart rate were the first and only positive, objective signs elicited aside from a short period of maternal hypotension. Therefore, if the presence of intraperitoneal blood is not the cause of the semitonic uterus, its presence in our case cannot be explained in the light of our present knowledge.

Analysis of 33 Reported Cases

Analysis of 33 cases of rupture of the spleen in pregnancy disclosed the following:

I. Rupture of the Spleen in Relation to the Duration of Pregnancy.—

The only conclusion that can be drawn from these statistics is the increased incidence of rupture of the spleen in the later months of pregnancy (Table I).

TABLE I. RUPTURE OF THE SPLEEN IN RELATION TO DURATION OF PREGNANCY

DURATION OF PREGNANCY	NO. OF CASES
3 to 5 months	6
6 to 8 months	9 (1 in labor at 7 months)
Term, not in labor	9
Term, in labor	5
Puerperium	3
Unknown	1
Total	33

II. Traumatic Rupture of the Spleen in Relation to the Duration of Pregnancy.—The type of trauma, presence or absence of inherent disease of the spleen and type of splenic pathology are shown in Table II.

TABLE II. TRAUMATIC RUPTURE OF THE SPLEEN IN RELATION TO DURATION OF PREGNANCY

DURATION OF PREGNANCY	NO.	CAUSE	NORMAL	DISEASE
5 months	1	Coitus	1	
6 months	1	Kick		Old splenic abscess
7 months	1	Blow	1	
7½ months	1	?		Malaria
8½ months	1	?	1	
9 months	3	1 Stretching to put out light	1	
		1 Blow	1	
		1 Fall	1	
Total	8		6	2

Of the 33 reported cases a history of trauma was obtained in 8. The trauma varied from a blow directed to the region of the spleen, to stretching to put out an overhead light at nine months' gestation, to coitus at the fifth month of gestation. Six spleens were reported as normal and 2 showed inherent disease, one malaria and one an old abscess. These statistics seem to indicate:

1. An increased incidence of traumatic rupture of the spleen late in pregnancy. Four of the 8 traumatic ruptures occurred after the viability of the baby.

2. The possibility of occurrence of rupture as a result of minimal trauma; for example, coitus, stretching.

3. A ratio in traumatic rupture of the spleen between normal and pathological spleens of 3 to 1, as 6 of the 8 traumatic ruptures occurred in normal spleens.

III. Spontaneous Ruptures of the Spleen in Relation to Duration of Pregnancy.—The presence or absence of inherent disease of the spleen and type of disease are shown in Table III.

TABLE III. SPONTANEOUS RUPTURE OF THE SPLEEN IN RELATION TO DURATION OF PREGNANCY

DURATION OF PREGNANCY	NO.	NORMAL	DISEASE
2 months	1	1	
3 months	3	1	1 acute splenitis, 1 Banti's disease
5 months	1	?	?
6 months	1	?	?
7 months	3	1	1 malaria, 1 spleen enlarged (in labor)
8 months	1		Thrombosis of splenic vein
9 months	8	7 (2 in labor)	1 malaria
Total	18	10	6

Of the 33 reported cases of rupture in pregnancy 18 are stated to have occurred unassociated with trauma and are, therefore, classified as spontaneous ruptures. Of these 18 cases we have pathological reports on 16 of which 10 spleens are said to have been normal and 10 to have shown disease. In 2 cases there was malaria, in one acute splenitis, in one Banti's disease, in one thrombosis of the splenic vein, and one spleen was simply reported as enlarged. From these figures, we therefore must conclude that:

1. Spontaneous ruptures of the spleen in pregnancy are more than twice as common as traumatic ruptures—18 spontaneous, 8 traumatic.

2. The ratio in nontraumatic ruptures between normal spleens and those revealing inherent disease is less than 2 to 1.

If, however, we consider, in the spontaneous group, only those spleens that ruptured after viability of the fetus, of which there were 9, 7 reported as normal and only 2 as diseased, we arrive at a ratio of 3 plus to 1 between normal and diseased spleens that rupture in this select group. This ratio is almost identical with the ratio in the traumatic group, which has been calculated as 3 to 1.

We feel the predominance of ruptures of the spleen, both traumatic and spontaneous, and the similarity in the ratio between the normal and pathological spleens in both groups late in pregnancy to be significant. We have consulted with numerous surgeons of repute on this subject and all are of the opinion that spontaneous rupture of a normal spleen occurs but rarely.

Byrne⁷ has stated categorically that a normal spleen never ruptures spontaneously. On the other hand, Zinkerman and Jacobi⁸ insist that although nontraumatic rupture of the normal spleen occurs infrequently, such a thing may happen. In this opinion others⁹ concur.

It is our opinion that numerous cases of rupture of the spleen in pregnancy, classified as spontaneous, are in reality cases of traumatic rupture in which the trauma was so minimal as to be overlooked or forgotten entirely.

McIndoe¹⁰ in 1932 was the first writer to bring to the attention of the medical profession the time interval frequently occurring between the original trauma directed to the spleen and signs of intraperitoneal hemorrhage. He reported intervals of from forty-eight hours to six months.

Zabinski and Harkins¹¹ stated that a time interval occurred in 14 per cent of the 181 cases reviewed by them.

Moore¹² cited the same figure and stated that in the 14 per cent in which there was a quiescent period, the trauma was slight.

All authors¹⁰⁻¹² reported that during the interval the patient is frequently symptom free.

It seems logical, therefore, in view of the fact that the vast majority of ruptures in pregnancy, whether traumatic or spontaneous, or occurring in normal or pathological spleens, do so late in gestation, that the presence of the pregnant uterus, with its associated physiological elevation of the diaphragm, renders the spleen more susceptible to rupture. This tendency becomes more logical if the presence of a short splenic pedicle, a splenic sulcus of unusual depth, and a short ligamentary attachment of the spleen to the left crux of the diaphragm in certain cases is kept in mind. A combination of a large uterus, a deep splenic sulcus, a short splenic pedicle and diaphragmatic ligament could mean rupture in the presence of extremely minimal trauma.

Diagnosis and Treatment

Aside from a history of trauma directed to the splenic area, the symptoms and physical signs of intraperitoneal hemorrhage, the results of rupture

of the splenic capsule in the pregnant state are not very different from those of any other condition associated with intraperitoneal bleeding under similar circumstances, for example, ectopic gestation, ruptured uterus before the onset of labor, rupture of an ovarian vein or veins in the pampiniform plexus. One must, however, keep in mind the minimal, and, at times, forgotten trauma necessary to produce intracapsular splenic hemorrhage and the time interval that frequently ensues between this trauma, with resultant intracapsular bleeding and disruption of the splenic capsule, and gross intraperitoneal hemorrhage.

Byrne⁷ stated the triad of epigastric pain, epigastric tenderness, and pain in the left shoulder (Kehr's sign) to be almost pathognomonic of rupture of the spleen. He added that aggravation of the pain on deep breathing or coughing is an important additional subjective symptom.

Larghero¹³ cautioned not to be misled by a relatively normal pulse, blood pressure, hemoglobin, hematocrit, and red cell count in evaluating a case of possible rupture of the spleen.

We feel that the mere thinking of this possibility in a pregnant woman with indefinite upper abdominal and/or back pains is of the utmost importance in making a diagnosis, even in the absence of a definite history of trauma.

Upper abdominal paracentesis is almost always positive for blood in a case of rupture of the splenic capsule and is an important and practical diagnostic procedure, provided the gravid uterus does not encroach upon the area to be tapped.

The value of x-ray as an aid in making a diagnosis, either prior to or after disruption of the capsule, is minimal, especially if the pregnancy is well advanced.

The treatment, of course, is splenectomy.

If the pregnancy has progressed to the point of viability of the fetus, or if it interferes in any way with the surgical approach to the spleen, a classical cesarean section should be performed prior to the splenectomy.

The postoperative care is for the most part routine. It is advisable not to ambulate these patients for 48 hours because of the fragility of the vessels in the splenic fossa and in the incised mesentery. For the same reason the possibility of vomiting should be circumvented by withholding food for at least 36 to 48 hours.

We would caution against: (1) placing too much reliability on the blood picture immediately following operation, (2) failure to keep the patients in electrolyte and protein balance, and (3) failure to be on the alert for pulmonary atelectasis. This is a common complication following splenic surgery for obvious reasons.

There is no postoperative sequela, the aftermath of splenectomy. The extensive reticuloendothelial system adequately compensates for the loss of its principal component.

Beck¹⁴ stated that after splenectomy women conceive, carry, and bear children without complications referable to the loss of the spleen. They do, however, develop general glandular adenopathies in the latter half of subsequent pregnancies which regress following delivery.

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Case Reports, New Instruments and Methods

CARPAL TUNNEL SYNDROME IN PREGNANCY

A Report of Two Cases

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ONE of the usually minor but occasionally disabling syndromes which has plagued pregnant women and their obstetricians for generations is so-called acroparesthesia or paresthesia of the extremities. While seldom serious, the symptoms of this syndrome are most annoying and bothersome to all concerned. These symptoms are numbness, tingling, pain, and at times even loss of sensation. When the upper extremities are involved, the symptoms may give rise to awkwardness and clumsiness in the handling of utensils. Deep-seated infections of the fingers have resulted from unnoticed puncture wounds from safety pins incurred by women in pinning diapers on their babies. The symptoms usually disappear promptly after the birth of the baby, but occasionally persist for weeks or months. Rarely some of them are permanent.

These neuritides, if they may be so called, which are peculiar to pregnancy and particularly when confined to the upper extremities, have been thought by many to be due to vitamin deficiency, particularly of fraction one of the B complex, thiamin. It has seemed strange to some more skeptical obstetricians, however, that, if this is true, we have not had better results from the administration of this vitamin in these patients.

This syndrome in the lower extremities has been ascribed to pressure from the pregnant uterus upon nerves of the pelvis. It has been suggested that pressure on the axillary nerves caused by the weight of enlarged breasts due to pregnancy may at times be responsible for the syndrome in the upper extremities. We have on record one case where such symptoms appeared six weeks post partum concomitant with the increased weight and surrounding edema of the breasts due to suppurative mastitis. Interestingly enough, though the patient had had no symptoms of this condition during the antepartum course of this first pregnancy, they appeared fairly early in her second pregnancy.

Our attention has been still more sharply focused on pressure as a cause of such symptoms by the cases now to be reported.

CASE 1.—Mrs. G. A., aged 31 years, first presented herself at the office of the senior author on Jan. 3, 1955, in the ninth week of her first pregnancy. Her weight at that time was 168 pounds. One month later her weight was 172 pounds, a gain of 4 pounds. The following month, when she was in the eighteenth week of pregnancy, her weight was 178, a gain of 6 pounds. Edema of the hands was quite apparent at this time and she was complaining of pain and numbness of the right hand and arm. She was placed on a low-carbohydrate and low-fat regimen with limitation of sodium and fluids. Thiamin chloride was prescribed for the neuritic symptoms, but incidentally gave no relief. About ten days after this visit the pain in the right hand became so intense that she was referred to Dr. A. W. Cook. For approximately seven years numbness had been observed intermittently in the lateral three fingers of the right hand. Shaking the hand allegedly would cause this abnormal sensation to disappear. There had been no change in this abnormal state until one month before admission to the hospital when the numbness became constant and was associated with weakness of the right hand, primarily the thumb, index, and middle fingers. The pain was increasingly severe over the volar aspect of the forearm, wrist, and thenar eminence and the lateral three fingers. There had been no pain in the left hand. The supine position seemed to aggravate the pain.



Fig. 1.—Photograph of the hands of the patient reported in Case 1 to show atrophy of the muscles of the thenar eminence in the right hand.

Physical examination disclosed the arterial blood pressure to be 100/68. There was mild protuberance of the abdomen compatible with a five months' pregnancy. There was mild edema of the lower extremities. The other pertinent physical features were confined to the right upper extremity and here there was mild swelling about the right wrist and forearm with dilatation of the veins over the volar aspect of the wrist. The skin of the right hand was dry and coarse compared to that on the left. There was weakness of the musculature of the right hand supplied by the median nerve distal to the wrist and there was hypalgesia over the sensory distribution of the median nerve of the right hand.

There was also obvious atrophy of the thenar eminence on the right and to a lesser degree on the left. Pressure over the median nerve at the wrist caused radiation of pain into the right index finger. Since the clinical features were indicative of a median nerve lesion at the wrist and other focal features suggested a lesion here, operation was carried out on April 4, 1955. The carpal ligament was found to be greatly attenuated at its medial aspect but on its lateral aspect it was abnormally thickened. The lateral attachment of the ligament was deep to the flexor pollicis longus tendon. The ligament was divided completely and the underlying median nerve was found to be edematous and soft. The day following operation pain was no longer present although sensory disturbance persisted. Following the patient's discharge from the hospital the sensory deficit remained and occasionally there has been trouble with "pins and needles" in the hand, but severe pain has never returned. In the third trimester of pregnancy pain of a mild character and "numbness" appeared in the left hand and were almost identical with what had been present on the right. These abnormal features persisted until after delivery when the greater part disappeared. The pain was never so severe in the left hand as to warrant surgical interference.

The remainder of the patient's prenatal course was relatively uneventful except for marked edema of the feet and ankles which failed to respond to the measures usually employed to alleviate this condition. At term, she had a normal labor and delivery of a 2,920 gram baby. The postpartum course was uneventful. Her symptoms had entirely disappeared at six weeks post partum.

CASE 2.—Subsequent to the delivery of this patient, her sister, who exhibited some of the permanent sequelae of this syndrome, was seen by Dr. Cook. During the first 3 of her pregnancies there had been no difficulties, but with the fourth, fifth, sixth, seventh, and eighth pain appeared primarily in the right hand and to some extent in the left hand. This usually appeared about the fourth or fifth month of pregnancy and remained until some two months post partum. In fact, the disability was such as to preclude her caring for her other children in these early postpartum months. The discomfort in the hand was described as of "boiling water" on the fingers of the right hand particularly. At times she could not feed or dress herself. When using the telephone she had to throw the phone from one hand to the other. It was also noted that she was unable to close a safety pin because of weakness.

Examination in the nonpregnant state disclosed mild atrophy of the thenar muscles of the right hand with mild weakness of this muscle group. There was marked hypalgesia over the entire distribution of the sensory branches of the median nerve in the right hand. However, the patient seemingly was unaware of this defect until it was demonstrated to her. Here, too, the abnormal neurological features were indicative of implication of the median nerve at the level of the wrist, possibly caused, as with her sister, by an anatomical anomaly of the carpal ligament.

The clinical features resulting from compression of the median nerve by the volar carpal retinaculum have been recorded by various authors. It has been seen in association with bony abnormalities about the wrist joint such as fracture or arthritis. The spontaneous occurrences of this syndrome were probably first recognized by Ramsey Hunt.² His patients, however, apparently manifested only abnormal motor features. Subsequently, Woltman,⁶ Zachary,⁷ Brain,¹ Vicale and Scarff,⁵ Kremer and associates³ and others have contributed to our knowledge regarding not only the principal clinical manifestations but also the pathogenesis of this form of so-called compressive neuritis. Subjective and objective disturbances of the median nerve in the hand constitute the significant abnormalities. There is painful tingling in the hand, especially at night, associated with aching up to the elbow and even the shoulder. Swelling may be evident in the proximal forearm as well as at the wrist. Neurological examination will disclose, in addition to various disturbances in sensibility over the hand, weakness, atrophy of the abductor pollicis brevis and opponens

pollicis muscles. Ischemia of the compressed nerve has been alleged to be the subtending factor in the syndrome and it has been suggested that endocrine features may assume some significance by increasing the volume of the content of the carpal canal.⁶

It appears that greater attention should be paid to detecting and relieving nerve pressure, by whatever means, in the treatment of these symptoms in pregnant women.

Addendum.—Since the completion of the above abstracts Dr. Cook has seen another patient who exhibited symptoms and signs almost identical with those experienced by the patient cited in Case 2.

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A CASE OF CARCINOMA OF THE RECTUM COMPLICATING PREGNANCY AND A REVIEW OF THE LITERATURE

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PRIMARY carcinoma of the rectum is a rare complication of pregnancy. It is indeed described, but briefly, in most standard textbooks of obstetrics.¹ Peller² stated that the incidence of all types of cancer in pregnancy is 4 to 6 cases in 10,000. The fact that malignant disease is being increasingly detected and that carcinoma of the rectum ranks fifth on the list of primary sites of carcinoma³ should make one conscious of its association with pregnancy.

To Jean Cruveilhier,⁴ 1837, must go the credit for reporting the first case of carcinoma of the rectum in the pregnant woman. Subsequently, several other cases were detected, and in 1908, Mlle. Tchegotarewsky,⁵ in her work, "Dystocie par tumeurs du rectum," presented a review of 35 cases. In March, 1952, Jennings,⁶ having culled the literature, reported 77 cases in addition to his own case; shortly thereafter, Berio, Hereter and associates⁷ reported two cases. The relative rarity of this complication of pregnancy and the interest engendered in the management of the condition make the reporting of this case worthy of note.

Report of Case

Mrs. R. C., a 48-year-old white woman, was admitted to the hospital surgical service on Feb. 2, 1955, because of marked prolapse of the rectum. The patient stated that she had first noticed this condition several hours prior to admission. About two and a half months previously, she had had several episodes of diarrhea with blood in the stool. There was no complaint of abdominal pain. Her last menstrual period occurred on May 14, 1954, and on admission she was at approximately 36 weeks' gestation. This was her nineteenth pregnancy, and she had had 18 previous normal, full-term deliveries. She had received no prenatal care and inasmuch as nearly all of her babies were born at home, she resisted all efforts to keep her in the hospital. As soon as the prolapse was successfully repositioned, she left against advice. The patient had been seen on obstetrical consultation and sixteen days later, heeding medical advice, she returned to the obstetrical service.

The patient was a well-developed, well-nourished white Italian woman about 38 weeks pregnant. The blood pressure was 130/70. Examination of the abdomen revealed the uterus to be 7 to 8 cm. below the xiphoid process, and the fetal heart was heard in the right upper quadrant at the rate of 128 per minute. Vaginal examination showed normally congested mucosa of the cervix and vagina; the rectovaginal septum showed no involvement. The cervix was found to be 1.5 cm. thick and 1 cm. dilated. Rectal examination demonstrated an annular mass 10 by 8 cm. with a friable cauliflower-like appearing area 4 by 3 cm. (Fig. 1). Lymph nodes could not be palpated.

Biopsy disclosed an infiltrating adenocarcinoma of the rectum, Grade III. Roentgen examination of the chest was normal, and examination of the abdomen showed no evidence of obstruction at this time. An electrocardiogram was normal. Results of

urinalysis were negative. Blood studies showed a red blood cell count of 2.7 million per cubic millimeter; a hemoglobin value of 7 Gm. per 100 c.c., and a white blood cell count of 8,850 with normal differential count. Urea nitrogen was 11 mg. per 100 c.c. Total protein was 5.5 Gm. per 100 c.c., with an albumin-globulin ratio of 1.7.

Clinical Course.—On Feb. 20, 1955, the patient received a transfusion of 500 c.c. of whole blood. She was seen by the proctologist in consultation, and this time the prolapse could be reduced without any difficulty. It was decided to deliver the patient vaginally, while taking all possible precautions to prevent contamination of the operative field by the prolapse. Prior to the onset of labor, the rectal mass was not visible, but after strong uterine contractions began, the mass was again extruded and remained visible. On Feb. 23, 1955, the patient was delivered, after a right mediolateral episiotomy, of a living male infant weighing 5 pounds, 10 ounces by frank breech.

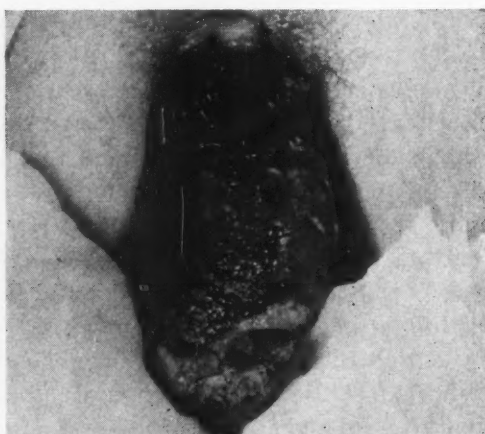


Fig. 1.—Prolapse of rectum with adenocarcinoma at distal portion. (Photograph taken in thirty-eighth week of pregnancy.)

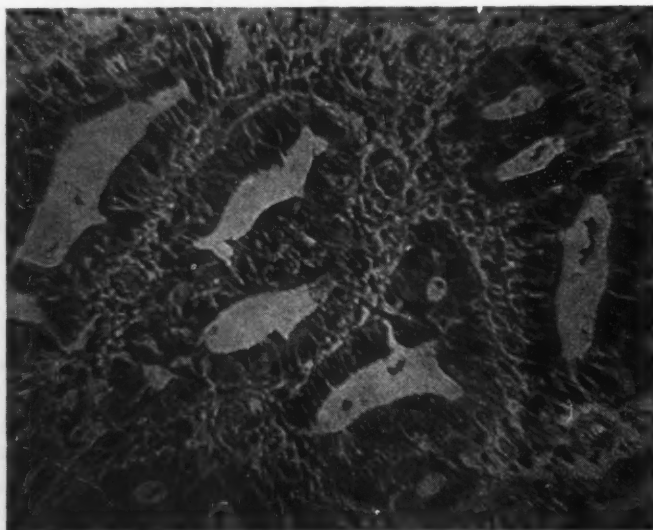


Fig. 2.—In the deeper areas of the tissue, a haphazard invasion of the submucosa with irregular gland acini is seen. The acini are lined by heaped-up columnar cells, which exhibit hyperchromatism, irregular nuclear patterns with chromatin dispersion, and scattered mitotic figures. Many of the acini reveal infolding of the multi-layered lining cells. There is no evidence of mucinous change. The tumor appears to remain differentiated with continuous infiltrating bizarre acini into the deeper submucosa. *Diagnosis:* Adenocarcinoma, infiltrating, differentiated, of rectum.

The prolapsed rectal mass was shielded from the operative field by sterile towels soaked in saline. The presenting part was delivered to the umbilicus and an assisted breech extraction was performed. No undue difficulty was encountered in the delivery. The patient had an uneventful postpartum course and was given another transfusion of 500 c.c. of whole blood on the third postpartum day. A barium enema, x-ray, and metastatic bone series were done on Feb. 26, 1955. A filling defect in the rectum, indicative of neoplasm, was reported; there was no evidence of bone metastasis. An alkaline phosphatase of 5.4 Bodansky units and a bilirubin of 0.1 mg. per 100 c.c. were reported.

Prior to discharge, the patient was instructed as to the gravity of her medical situation and arrangements were made for her to have surgical treatment in two weeks. She was adamant in her refusal to submit to surgery. She was visited on several occasions in her home and when last observed in September, 1955, six months post partum, had lost no weight and had no subjective complaints. Attempts are still made to follow this woman on an outpatient basis in order to obtain further studies.

Comment

Until this present case, carcinoma of the rectum had never before been reported in a patient of such extensive multiparity and of such an age. The age group had previously ranged from 18 years in Nijhoff's⁸ patient to 43 years in Heusner's.⁹

Most standard texts advocate radical operation if the condition is detected early in pregnancy. Munro Kerr, Johnstone, and Young¹⁰ stated that "if the condition is operable a radical operation be performed, and if inoperable pregnancy be allowed to continue." They further state that if the lesion causes obstruction, a cesarean section is the operation of choice. In reference to obstruction in pregnancy, this condition has been reported in only 8 cases.¹¹⁻¹⁷

The first recorded case of carcinoma of the colon producing obstruction in pregnancy with survival of mother and baby was presented by Finn and Lord¹⁶ in 1945. A three-stage operative procedure, consisting of a preliminary transverse colostomy with later resection of the growth and end-to-end aseptic anastomosis was instituted. If obstruction occurs early in pregnancy, it is most strongly advocated that immediate hysterectomy, colostomy, and later resection be done.¹⁸ We believe that if bowel obstruction occurs during pregnancy, heroic measures should be employed in the treatment of the acute obstruction and that the pregnancy should be managed according to obstetrical indications.

The recommendation that the pregnancy should immediately be interrupted as soon as the diagnosis has been made is found in the older literature. The more recent literature indicates that extragenital cancer (except in the breast) is not influenced by pregnancy, and Slye¹⁹ has found that there is a retardation of tumor growth during pregnancy. It has been asserted that carcinomas of the colon and rectum grow more rapidly and metastasize earlier in young people. Buser, Kirsner, and Palmer²⁰ found no correlation between age and survival time in patients with malignancy of the large bowel.

Until the present moment, our patient, despite all persuasion, has refused to permit operation to be performed. In this regard, Daland, Welch, and Nathanson²¹ in 1936 obtained a statistical figure of the median duration of life in untreated cases of carcinoma of the rectum of 14 months and came to the

conclusion that colostomy alone or colostomy with radiation (x-ray) did not prolong life appreciably in comparison with the life duration in untreated cases. Grinnell,²² in an analysis of more than 2,000 cases treated during a 35 year period (1916-1945), found that the absolute 5 year survival rate for patients with carcinoma of the rectum is 25.6 per cent and that the relative survival rate for patients who underwent abdominoperineal resections from 1916 to 1945 was 46.4 per cent. The 5 year survival rate for 53 patients with carcinoma of the rectum treated by colostomy and perineal proctectomy from 1916 to 1945 was 32.1 per cent. Hence, there is a 13.3 per cent increase in 5 year survival rates following abdominoperineal resection, although it is possible that this may not be a statistically valid difference.

Summary

A case report is presented of carcinoma of the rectum complicating pregnancy in a patient of the most advanced age yet described (48 years) and of the most extensive grand multiparity (19).

Prior to this report, 80 such cases have been previously described; this case makes a total of 81. In order to evaluate properly the handling of the case, one should always bear in mind the stage of the pregnancy. With this thought in mind and after being duly warned that each case must be individualized, we would suggest that:

1. In the early stages of pregnancy, the cancerous condition should be treated regardless of the fetus.
2. In the second trimester, if bowel obstruction does not occur and if the patient's general condition is good, a colostomy may be attempted, although this may not be necessary.
3. In the third trimester, medical induction is recommended with delivery per vaginam and, if there are no contraindications, followed in two weeks by an abdominoperineal resection.
4. At whatever stage of pregnancy, if bowel obstruction occurs, heroic measures must be undertaken in the treatment of the acute obstruction and the pregnancy be relegated to a secondary consideration.
5. Cesarean section should be done only for obstetrical indications.
6. Abdominoperineal resection is the operation of choice following the termination of the pregnancy.
7. Removal of the uterus is to be performed only if it is involved in the cancerous lesion.

In conclusion, one should be guided by the knowledge that approximately 50 per cent of carcinomas of the colon and the rectum are inoperable by the time of diagnosis. The physician must always bear in mind that the elderly obstetrical patient is a special candidate for neoplastic diseases, and that early diagnosis is imperative.

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A CASE OF TRIPLETS INCLUDING ANOMALOUS TWINS AND A FETUS COMPRESSUS*

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FETUS compressus or papyraceous has been described in medical literature for a great many years. Kindred¹ in 1944 described the important features of this condition and reviewed the literature. More recent papers are those of Posner and Klein,² Kerner,³ and Mulliken.⁴ X-ray diagnosis of fetus compressus has been reported.⁵ At least one case of fetus compressus has been reported in quadruplets.¹⁰ There have been at least 23 cases reported in triplets.⁶⁻⁹ We found among these 4 cases resembling ours, in that there were 2 liveborn infants plus one fetus compressus in each set of triplets.¹¹⁻¹⁴

Case Report

Mrs. M. R., a 27-year-old white woman, para 0, gravida iii, was admitted to the obstetrical floor at 8:30 A.M. of Christmas Day, 1955, in advanced labor.

The only significant events in the past history were two spontaneous first trimester abortions, in October, 1954, and February, 1955, with curettage following the second.

The last normal menstrual period before the present pregnancy began May 6, 1955, the due date being Feb. 13, 1956. This pregnancy had been uneventful with the following exceptions: (1) moderate ankle edema and blood pressure of high normal levels from September to November, 1955; (2) multiple pregnancy suspected at the patient's first office visit, Sept. 14, 1955, and confirmed three months later by an abdominal x-ray showing the presence of twins. (3) Rh-negative condition and mild anemia.

On admission the patient had been in active labor with ruptured membranes for one and a half hours. Abdominal palpation revealed twins, one apparently in cephalic presentation and the other breech. Fetal heart tones were audible on the right only, regular at 140 per minute. Rectal examination showed the cervix to be effaced and the os dilated 8 cm. with the presenting occiput at plus one station.

At 9:08 A.M. a living male infant was delivered spontaneously. The total length was 17 inches and weight 4 pounds, 4 ounces.

Fourteen minutes later the second liveborn male was delivered spontaneously as a frank breech, shortly after the second bag of waters had been artificially ruptured. This infant weighed 4 pounds, 4¼ ounces and was 16½ inches in total length.

Modified Credé expression of the placenta was attempted, when, at 9:29 A.M., an object the size and shape of an adult kidney was delivered. This proved to be a stillborn side-to-side compressed fetus covered by its amniotic sac. A few cubic centimeters of brownish fluid were found on opening this sac. The fetus was a male 10 inches (25 cm.) in total length and weighing 9 ounces (270 grams) (Fig. 1). Postmortem examination disclosed no visceral abnormalities and there was no mummification. The flattened umbilical cord was 20 cm. long and free at its distal end.

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The placenta was delivered at 9:36 A.M. It was a fused placenta with a four-layered septum demonstrable between the two fetal sacs. The membranes were closely adherent to the fetal surface of the center only of the placenta. At the center of the maternal surface was noted a large area of infarction. The umbilical cords of the liveborn babies were inserted at opposite ends of the placenta. No sign of the point of insertion of the third umbilical cord could be found.

Cord blood from the first of the triplets was type A, Rh positive (DeE), Coombs negative. Cord blood from the second infant was similar but type O. Blood taken from the superior sagittal sinus of the fetus compressus was type O, Rh not determinable.



Fig. 1.—A frontal view of the fetus compressus, showing marked side-to-side compression of the fetus as well as of the umbilical cord.

The firstborn baby appeared to be normal except for a deformed right external ear and absent right external auditory meatus (Fig. 2). He was discharged from the hospital at 4 weeks of age weighing 5 pounds, 3 ounces, and has remained in good health.

The second of the triplets was noted to have scaphocephaly and microcephaly (Fig. 3). He fed poorly, was much less active than his sibling, and showed incoordination of the extremities. He was discharged from the hospital at 5 weeks, weighing 5 pounds, 5 ounces, in fair condition, but died two weeks later, apparently of bronchopneumonia. No postmortem was done.

The mother was discharged from the hospital on the third postpartum day in good condition except for a marked anemia.



Fig. 2.—Deformity of the right external ear of the first infant.



Fig. 3.—Normal cranial contour of the first infant (left) compared with scaphocephalic head of the second infant (right).

Summary

We found this case to be interesting in that it presents the unusual condition of fetus compressus in a triplet pregnancy with the other fetuses liveborn but congenitally abnormal. This is a triamniotic, dichorionic pregnancy with the two liveborn infants being fraternal triplets and probably the second liveborn identical with the fetus compressus.

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VAGINAL DELIVERY IN A PARAPLEGIC PATIENT

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IN ORDER to clarify all factors inherent in pregnancy and its complications, expulsion of the fetus, and relief of pain, during the past quarter century medical research has focused its attention on the study of the female genital tract. A thorough understanding of the musculature and topographic location and specific function of each neuromuscular pathway to all organs has been undertaken.

During a review of the literature it was found that investigation of uterine innervation and physiology has been carried on since 1732. It was discussed by Winslow in the eighteenth century; Tiedemann, Bourguery, Frankenhauser, and Rein in the nineteenth century; and numerous others in the twentieth century.

Sir James Simpson, in 1871, found normal parturition in sows after removal of the thoracic and lumbar cord, except that the last fetus of the litter remained in the vagina. In the same year, Rieman, upon performing a similar experiment, found the same thing to be true, as did Rein, ten years later, following section of all extrinsic uterine nerves. In 1924, Good,⁶ after observing a case of pregnancy and labor complicated by spinal cord injury and reviewing the literature, concluded that the sympathetic nervous system and not the spinal cord controls uterine contractions. Canon, in 1929, described parturition in a cat six weeks after the exclusion of all sympathetic impulses by removal of the sympathetic ganglia. A few years later, Fontaine and Hermann⁵ testified to parturition with normal delivery in a patient who had undergone resection of the superior hypogastric plexus for dysmenorrhea.

Cushney's experiments on mammals, early in the twentieth century, established the fact that automatic, rhythmic uterine contractions are myogenic rather than neurogenic and demonstrated completion of the first stage of labor after severance of all uterine nerves. This was confirmed by Clark⁸ in 1911. More recently, Nilson⁹ reported a case of pregnancy and spontaneous labor devoid of first and second stage complications in a quadriplegic patient confined to a respirator. However, absence of secondary forces necessitated a low forceps extraction.

Physiology of the Uterus in Labor

Hofbauer,⁷ who in 1929 described the normal and abnormal responses of the uterine musculature in pregnancy and labor, believed that a mechanism analogous to the Purkinje or conductive system of the heart exists. He described a mesial bank, thinning out laterally on the anterior wall of the uterus and two thin longitudinally arranged bundles on the posterior wall. He quotes the following observation of the uterus after intramuscular injection of

Pituitrin during cesarean section: "A pale band from two to three inches wide, composed of parallel fibers, is visible over the anterior surface of the uterus all the way from the bladder reflection to the fundus in its pattern resembling the teniae of the large intestine. The wave of contraction spreads from this band and involves an ever increasing area of the pregnant organ. Synchronous with the first appearance of the tenia in the midline, there comes into view an orbicular structure surrounding the insertion of the tubes, as well as a pale zone in the midline of the posterior aspect of the lower uterine segment. These phenomena are most striking when the operation is being performed under spinal anesthesia."

Later investigations into the physiology of the mammalian uterus in labor by Rudolph and Ivy⁸ led to the comparison of the mechanism in the corpus uteri of the dog with that found in the heart. It is known that the stomach manifests receptive relaxation as food enters, after which it moves to evacuate its contents according to a definite polarity. In a similar manner the corpus uteri dilates to receive the fetus, and when the cavity is full, contracts to expel it. It is generally accepted that the action of the abdominal muscles and diaphragm raises the intra-abdominal pressure and thus facilitates expulsion of the fetus. The dog manifests the "bearing down" phenomenon, as does the human organism, when the fetus is in the vagina. The absence of this phenomenon in cases of low thoracic section is of significance.

Evidence of an intrinsic nervous mechanism in the uterus, observed as a network of nerve fibers in the uterine wall, was reported by Flemming. However, no nerve cells resembling those in the sympathetic ganglia were found. As a result of his observations of the action of drugs and histologic studies of the uterus, he stated that there is "some arrangement for the control of tone and movement distributed at different levels." Although the question of the role played by a hormone or hormones in the initiation of labor and the uterine hypertrophy of pregnancy cannot be disregarded, it is unlikely that they are a basic factor in the causation of the coordinated activity of the uterus in labor. Supporting the work of Hofbauer, Rudolph, and Ivy is the fact that the uterine muscle will contract rhythmically in Locke's solution. Also, experiments on dogs and rabbits have shown that the musculature in the placental site is less involved in the uterine contraction and, in fact, exercises an inhibitory action on the local coordinating mechanism or muscle fibers.

Asymmetric contractions and tonus states of the uterus, as well as isolated contractions, may be attributed to the assumption that defective embryologic fusion of the urogenital folds and Müllerian ducts gives rise to various types of uteri.

Although uterine contractions have been evident in poliomyelitis victims with paraplegia and quadriplegia,⁹ as well as in patients paralyzed as a consequence of tumors of the cervical¹ and thoracic cord,⁶ many questions relative to the mechanism of uterine contractions remain to be answered.

Report of a Case

On Dec. 15, 1955, a 24-year-old gravida ii, para i, paraplegic woman was admitted in active labor.

Ten years previously, due to a fall from the roof of a house, the patient sustained a fracture of the thoracic spine. The resulting paraplegia of the lower extremities and urinary and fecal incontinence were complicated by severe decubitus ulcers of the buttocks, osteomyelitis of both hips, more pronounced on the right side according to x-ray, and urinary infection. These conditions were treated on several occasions but recurred repeatedly. Two years previously the patient was delivered of a living infant.

On this admission the vital signs were within normal limits. Physical examination showed no pathological conditions of the upper third of the body. A large decubitus ulcer was observed over the sacrum, and multiple scars of the previous osteomyelitis were scattered over the pelvic area. Abdominal, cremasteric, and lower extremity reflexes were absent. The skin of the lower extremities was tense and shining, a flaccid paralysis being exhibited. The vaginal opening was located about 3 cm. below both hypertrophic labia. Due to the presence of a retention catheter over a period of years, the urinary meatus was abnormally large. Uterine contractions were palpated.

The patient stated that she had come to the hospital because of an unusual sensation, which she thought must be labor pains, in her abdomen. She appeared to be in no acute distress. Upon pelvic examination the cervix was found to be fully dilated and the fetal head at the symphysis. After a left lateral episiotomy, she was delivered of a living infant. However, because the patient was unable to expel the baby, a low forceps extraction of the fetal head was necessary.

Surgical aseptic technique was maintained, as nearly as possible, during delivery. Immediately after, a retention catheter was reinserted and the bladder irrigated with normal saline twice daily during the period of hospitalization. Prior to admission, the decubitus ulcer was treated with Polysporin ointment. Combiotic, 2 c.c. daily, and Terramycin, 250 mg. every 6 hours, were given until her discharge from the hospital. The episiotomy healed well. Upon request, the patient breast fed her baby.

Both left the hospital in good condition on the fourth postpartum day.

Comment

1. It is obvious from research and reports of cases that the uterus will contract in spite of division of the spinal cord and severance of the sympathetic nerve supply to the uterus.
2. Paraplegia in a pregnant woman is not an indication for cesarean section.
3. Repeated pregnancies in a paraplegic woman are not contraindicated from an obstetrical point of view if the patient's prenatal course can be closely followed.
4. A case of multiparity in a paraplegic patient whose delivery and puerperium were normal has been reported.

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CHORIOANGIOPAGUS PARASITICUS (SCHWALBE)

Report of a Case of Acardius Acephalus and of a Case of Fetus Amorphus

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THE acardius is a variety of monster intimately related to monovular twins. In order that the acardius, or heartless monster, may live, it must receive its blood supply from the normal twin with a functioning heart. According to Schwalbe¹ an acardius is a free, parasitic double monstrosity, the chorioangiopagus parasiticus. This definition is well chosen because it emphasizes the complete parasitic dependence of the acardius on the circulatory system of the normal twin. This condition is not to be confused with that of fetus papyraceus or blighted fetus, in which a normal viable twin is born simultaneously with a small underdeveloped and compressed fetus. Schatz's² classification recognizes two groups of acardii: (1) hemiacardius and (2) holoacardius, and with the following subdivisions: (1) acardius acephalus, (2) acardius acormus, (3) acardius amorphus.

If the monster possesses a rudimentary heart he considers it a hemiacardius. A true holoacardius should possess no heart at all. There may be transitions between the two. The descriptive classification of the acardii is based mainly on gross anatomic appearance. The extremities may be either completely present or only partially defective in a hemiacardius. More or less striking malformations of other parts of the body could be present. The skin and soft tissues are usually saturated by serous fluid and have a spongy texture. The skeletal system could sometimes be remarkably well developed. The internal organs may show extensive malformations. The heart may show various stages of defective development. Malformations of the great vessels of the heart could be so extensive that their interpretation is difficult or impossible. Instead of equal twins being born there comes forth a single well-formed individual, accompanied by an amorphous lump of flesh contained in the same sac. It is recognizable as a product of conception only because it usually possesses a more or less distinctive umbilical cord. The cord being of rudimentary structure possesses only a single artery and a single vein. The vein brings the blood from the acardius into the umbilical circulatory system of the normal twin, while the artery represents one of the branches of the umbilical artery of the normal twin.

An *acardius acephalus* presents the lower half of the body, with limbs or parts thereof in various stages of development, but the head is entirely missing. The specimen of Case 1 belongs to this group. An *acardius acormus* has the head end existing alone as little more than a cherublike structure, the lower

half of the body being entirely missing, and the head attached directly by a rudimentary umbilical cord to the placenta. A *holoacardius amorphus*, represented in Case 2, is a completely shapeless mass, as a rule without any resemblance to human form. Dissection of such an outwardly shapeless mass may show, however, rudimentary anlage of internal organs and skeletal parts entirely unexpected by external examination. Schwalbe¹ described a well-formed femur found in an *acardius amorphus* not unlike that found in a mature fetus. The femur presented a well-defined epiphysis and diaphysis. This is an example of complete self-differentiation of a part of the embryonic anlage associated with rudimentary development of the rest of the embryo, as explained by Spemann's³ theory of induction and organization of embryonic development, which allows an independent development of each single part of the embryonic anlage.

CASE 1.—*Acardius acephalus*. Woman's Hospital Record No. 102630. The mother was a 21-year-old Negro para 0, gravida i. Her last menstrual period was on Dec. 10, 1948. The estimated date of confinement was Sept. 17, 1949. She was first seen on June 13, 1949, when transverse lie or multiple pregnancy was suspected. Her second visit was on July 18, 1949, when the uterus was estimated to be the size of a 7 months' pregnancy. At that time the fetal heart was not heard. On July 24, the patient was delivered spontaneously at home and the patient and the "specimen" were brought by ambulance to the hospital.

Following is the pathology report (Record Numbers 76084 and 221):

The placenta was intact and measured 15 by 13 by 1.5 cm. The maternal surface showed more or less complete obliteration of the contours of the individual cotyledons due apparently to necrosis. The fetal surface showed two umbilical cords. One of them was 21 cm. long connected with a macerated female fetus 20 cm. in length (weighing 80 grams). The cord was attached paramarginally about 4 cm. from the edge of the placenta. The second umbilical cord was only 2 cm. long. It showed a velementous insertion about 10 cm. from the insertion of the first-mentioned umbilical cord. There was, however, a large blood vessel connecting the sites of the insertion of both umbilical cords and running near the edge of the placenta. This second short umbilical cord was connected with a kidney-shaped monster measuring 10 by 8 by 2.5 cm. It consisted of a body, more or less rounded, with three projections representing apparently rudimentary extremities. There was no evidence of neck or head. The upper segment of the body of the monster showed a 2.5 cm. long projection which represented on closer inspection a rudimentary forearm terminated by two digitlike projections. The lower segment of the body presented two projections measuring 5 cm. in length and 2.5 cm. in diameter, respectively. Both projections terminated in footlike structures bearing resemblance to formed toes. The placenta with the attached monster weighed about 360 grams (Fig. 1).

Diagnosis: *Holoacardius acephalus*.

The specimen was examined by the X-ray Department of the Woman's Hospital, and the following is the x-ray report (Number B-994). The specimen included twin products of conception, one of which showed a normally formed skeleton and skull, except that at the vertex there were irregular folds, which might be either cranial soft tissue or overlapping sutures. The other item consisted of two parts, a loose mass of tissue and a more or less rounded tumorlike mass containing a good part of the fetal skeleton. The lumbar spine was normal. The thoracic spine was nearly normal with a few irregular vertebral bodies. The cervical spine was rudimentary. Ten ribs were made out with a little abnormality in the upper half of the left. Pelvic bones, one thigh bone, both tibiae and fibulae and one humerus were normal looking. Both scapulae were present although "peculiar" looking. There were a few phalanges irregularly disposed. No sign of a head was present (Fig. 2).

CASE 2.—*Acardius amorphus*. Woman's Hospital Record No. 105457. The patient was a 21-year-old white woman, para i, with a history of one abortion. Her last menstruation was on July 21, 1952, and the estimated date of confinement was April 20, 1953. She had no familial history of twinning or monstrosities. Her past history showed no record of serious illnesses. She made six antepartum visits to the maternity clinic. Her weight gain was recorded as 21 pounds and the antenatal course was uneventful. She was admitted to the hospital on April 14, 1953, because of premature rupture of the membranes and went into labor seven hours later. After six hours of labor she was delivered by prophy-

Fig. 1.

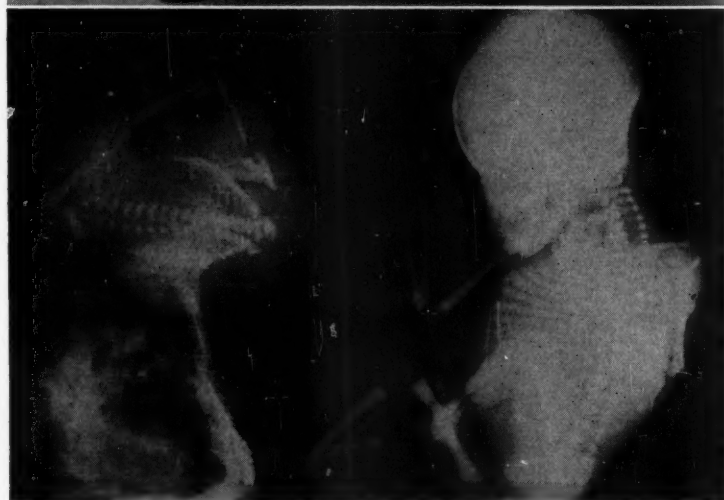


Fig. 2.

Fig. 1.—Holoacardius acephalus (lower left), macerated fetus, and single placenta.

Fig. 2.—X-ray photograph of Fig. 1 to show skeletal structures of holoacardius (upper left).

lactic low forceps of a living female child weighing 6 pounds and 2 ounces. Attached to the placenta, which was delivered spontaneously, was the amorphous tumor to be described below. This was attached to the placenta by another shorter umbilical cord. The postpartum course was uneventful. The patient and the baby left the hospital on the eighth postpartum day.

Following is the pathological record of the specimen which was sent to the laboratory (Path. No. 88282). The placenta measured 17 by 18 by 3 cm. The main umbilical cord was 46 cm. long and showed paramarginal insertion. About 6 cm. from the insertion of the umbilical cord continuous with one of the branchings of the large placental vessels was found another short umbilical cord which measured only 5 cm. in length and which was connected with an entirely round spherical structure covered with skin and measuring 10 cm. in diameter. The site of entrance of the rudimentary umbilical cord into the globular structure was marked by a nodule 2.5 cm. in diameter covered with wrinkled skin and showing hemorrhagic discoloration.

Fig. 3.

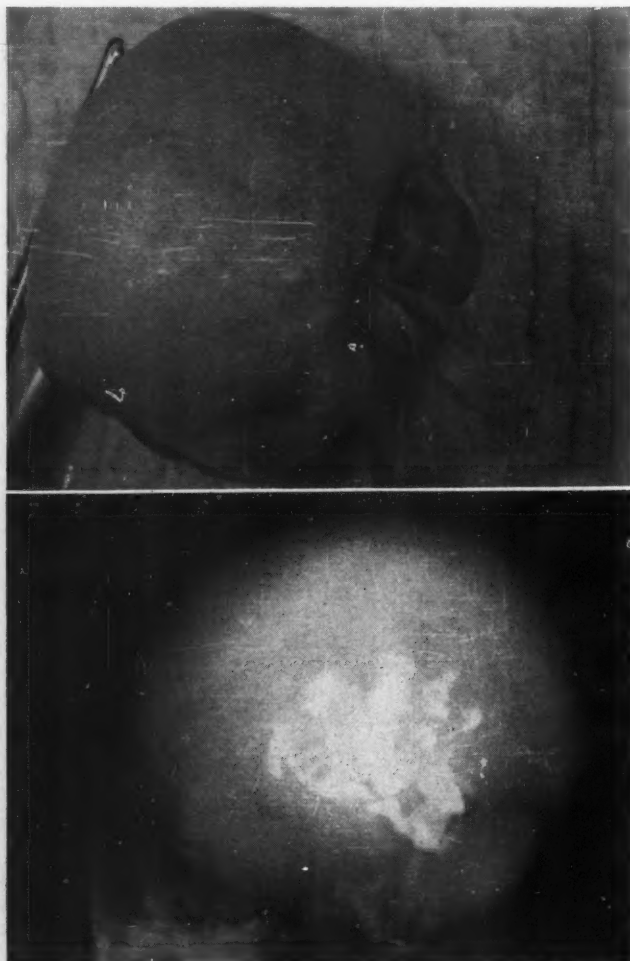


Fig. 4.

Fig. 3.—Holoacardius amorphus.

Fig. 4.—X-ray photograph of Fig. 3 to show bony structures contained in the body of the holoacardius.

Diagnosis: Holoacardius amorphus, twin placenta (monozygotic twins) (Fig. 3).

From the x-ray examination of the monster (No. F424) the following was recorded: The specimen consisted of placenta, umbilical cord, and a rudimentary fetal mass. A normal twin had been removed.

There was an ovoid soft-tissue mass measuring 9 by 7.5 cm. on the film, with a single small protuberance at its pole measuring about 2.5 by 1.5 cm. In the center of the mass

was a disorganized aggregate of bony parts. Several of these parts were identified as a scapula, a few ribs, parts of a bony pelvis, with irregular bony shapes which were probably an attempt at long bones. Other bony deposits could not be identified as any specific structure (Fig. 4).

The driving force behind the circulation of the acardius is the heart of the normal twin. There is an anastomosis between the efferent circulatory component of the acardius and the umbilical vein of the normal twin. This features a reversal in the usual direction of fetal blood flow, i.e., via the umbilical vein to the fetus and returning by the umbilical arteries. Hempel⁴ was the first to recognize the reversal of the circulation. Consequently, any accidental or more or less constant impediment in the venous return to the only heart of the so intimately interlocked circulatory systems of both twins results in critical, passive hyperemia in the acardiac twin. The passive venous congestion explains the marked edema and pseudohypertrophy of tissues of the acardiac twin. The increase in volume resulting from the peculiarities of reversed blood stream of the acardiac fetus may lead to critical difficulty in the delivery.

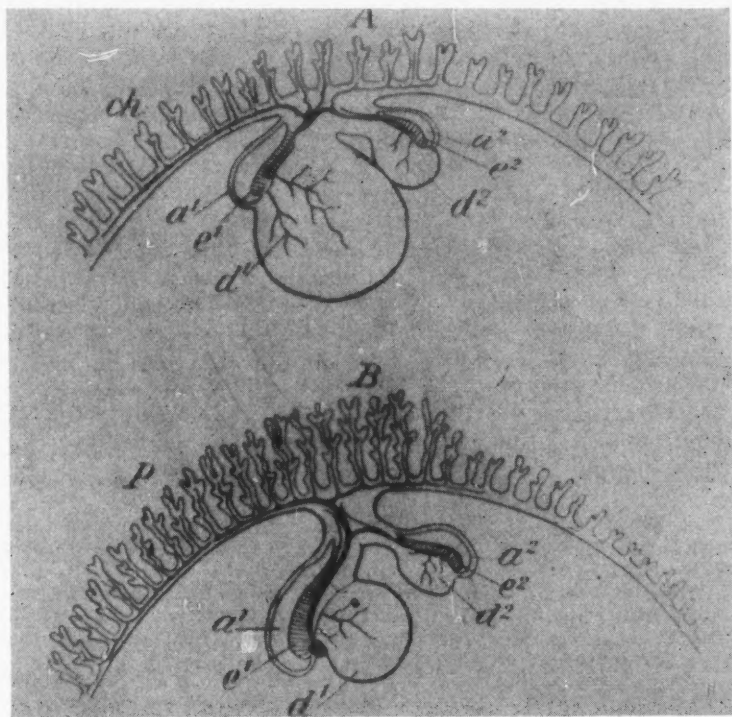


Fig. 5.—Marchand's scheme of mode of development of an acardiac monster.

The heart of the normal twin does not remain unaltered in the presence of this addition to its circulation. As in the case of an arteriovenous anastomosis, the heart of the normal twin is usually enlarged because of the additional burden created by the parasitic supplement of the circulatory system of the acardius.⁵ These conditions are usually reversible at birth with the severing of the umbilical cord.

Divergent theories explain the origin of the acardius. Briefly, these may be described under three headings: (1) Meckel,⁶ Dareste,⁷ and Panum⁸ believed in the primary deficiency in the assembly of germinal layers resulting

in failure of development of the heart in one twin, the acardius surviving only because of the presence of an anastomosis developed between the vessels of the two umbilical cords. The theory of primary defect in the arrangement of germinal layers is supported by the fact that most acardiacs originate at an early period of development. (2) Claudius⁹ and Ahlfeld¹⁰ believed that two evenly developed twin embryos were present initially with communicating circulations. Then, for some reason, the motor force of the heart of one twin overpowered that of the other and the heart of the weaker became more or less obliterated. The acardius thus became a sort of a parasitic partner of the normal twin, suffering in this partnership not only the gradual disintegration of the heart but also failure of development of other parts of the body. (3) Schatz and Marchand¹¹ suggested a primary defect of development as the cause of the acardius. Fig. 5, A shows Marchand's scheme of the mode of development of the acardiac monster. The chorion is already developed; the yolk sac has divided into two unequal halves. Consequently, one embryo receives through the yolk vessels more abundant nourishment than the other embryo. As a result its allantoic circulation develops more actively so that the later developing allantoic artery of the smaller embryo presents a mere anastomosis of the allantoic circulation of the normal twin. In the later stage (Fig. 5, B) the allantoic vessels of the larger embryo usurp the whole of the chorion. The smaller embryo gains its blood supply entirely through the anastomosis of its allantoic artery with that of the larger embryo. Therefore, the blood of the acardius circulates in the reverse direction to the normal current.

Summary

1. The variety of monsters that may develop as one member of a set of twins has been described.
2. Two case reports are given, in one of which the acardiac monster was born along with a macerated stillborn infant at about 28 weeks' gestation, and the second following the birth of a full-term normal child.
3. The theory of origin of the acardius was discussed with particular reference to the reversal of blood flow of the acardius in relation to the normal blood current of a normal fetus.

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A CASE OF A PELVIC TUMOR PRODUCED BY A URINARY TRACT ANOMALY

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THIS is a case report of a urinary tract anomaly presenting itself as a pelvic tumor. Brady¹ stated that "anyone doing abdominal surgery is apt to encounter an inflammatory condition or tumor which . . . will be extraperitoneal." A description of all extraperitoneal pelvic masses would "resemble a treatise on general pathology."² For simplicity, these tumors are divided into five groups: (1) true neoplasms, (2) cysts, (3) infections, (4) urinary tract anomalies, and (5) miscellany (hematomas).

S. J., No. 16993, a 17-year-old Negro woman, para 0, gravida 0, was admitted to the hospital Nov. 17, 1955, because of severe pain in the left lower quadrant and chills and fever for nine days. The pain started with the onset of menses. It radiated to the back and was relieved somewhat by flexing the left thigh. It had grown more intense for the past few days.

The patient had previously been admitted to another hospital 4½ years before for eight days. She had similar complaints at that time. The remainder of her history, including her menstrual history, was normal.

On examination, the patient had a temperature of 102.4° F., a pulse of 124, and a blood pressure of 120/80. The head, neck, heart, and lungs were normal. An exquisitely tender mass filled the left lower quadrant of the abdomen and there was rigidity and rebound tenderness over it. The rest of the abdomen was soft and nontender. There was no distention. Pelvic examination disclosed a soft cervix; the uterus could not be outlined due to a very tender cystic mass which filled the left fornix and cul-de-sac and seemed continuous with the mass felt abdominally. There was no induration of the rectovaginal septum.

The sedimentation rate was 18 mm. in 30 minutes. The hemoglobin was 10.7 Gm., and the white blood count was 17,850. A urinalysis was negative.

A presumptive diagnosis of an ovarian cyst with a complicating infection and/or torsion was made. An x-ray of the abdomen showed only the presence of a soft-tissue mass in the left lower quadrant.

For the next seventy-two hours, the patient's temperature fluctuated between 102.2° and 104.5° F., and she continued to have severe pain in the left lower quadrant. Peristaltic activity was normal but the abdominal signs persisted. Because of the lack of response to antibiotics and supportive therapy a laparotomy was performed.

The abdominal cavity did not contain an unusual amount of fluid and the pelvic organs appeared normal. Lying beneath the posterior leaf of the left broad ligament was a cystic mass measuring 10 cm. in diameter. This mass was first thought to be an intraligamentous cyst. As it was freed from the surrounding tissues, however, it was traced downward to the undersurface of the bladder. It tapered to a diameter of 3 cm. here and seemed to end as a blind pouch which invaginated the bladder wall. The tissues were quite indurated in this area, but the end of the mass was separated from the bladder by careful sharp and blunt dissection. Inspection showed no connection between it and the bladder cavity. While the mass was being freed, it was ruptured and about 750 c.c. of foul pus escaped.

The mass was then traced upward from its position behind the left broad ligament. It lay between the psoas muscle and the descending colon and extended all the way up to the diaphragm, to which it was intimately adherent. Its diameter here was narrowed to 3 cm. and it ended as a blind pouch here too. At about the level of the second or third

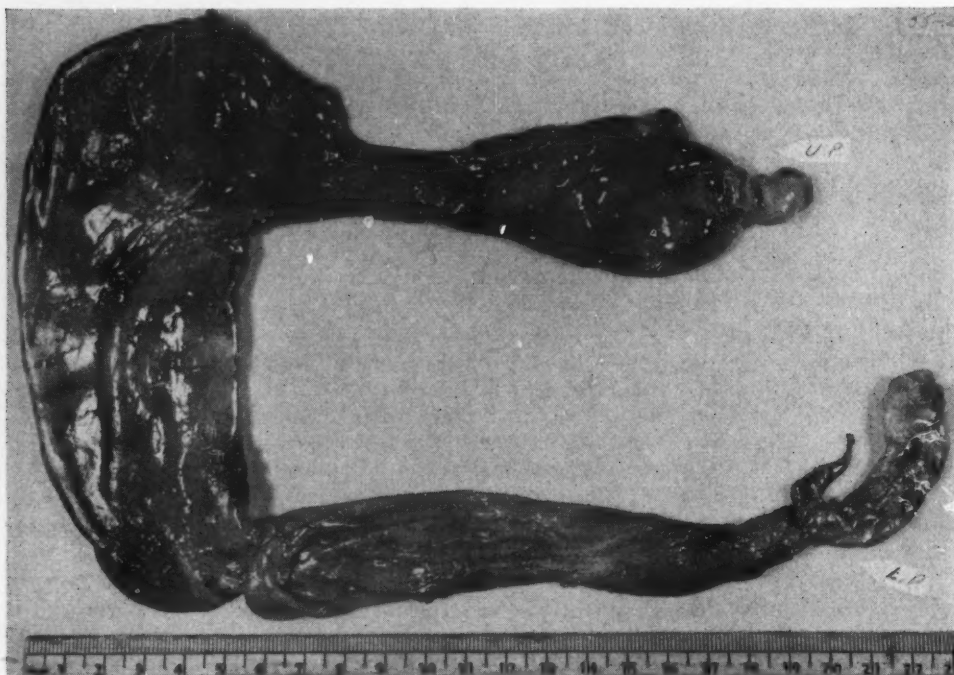


Fig. 1.—Gross specimen. U. P., upper pole; L. P., lower pole.

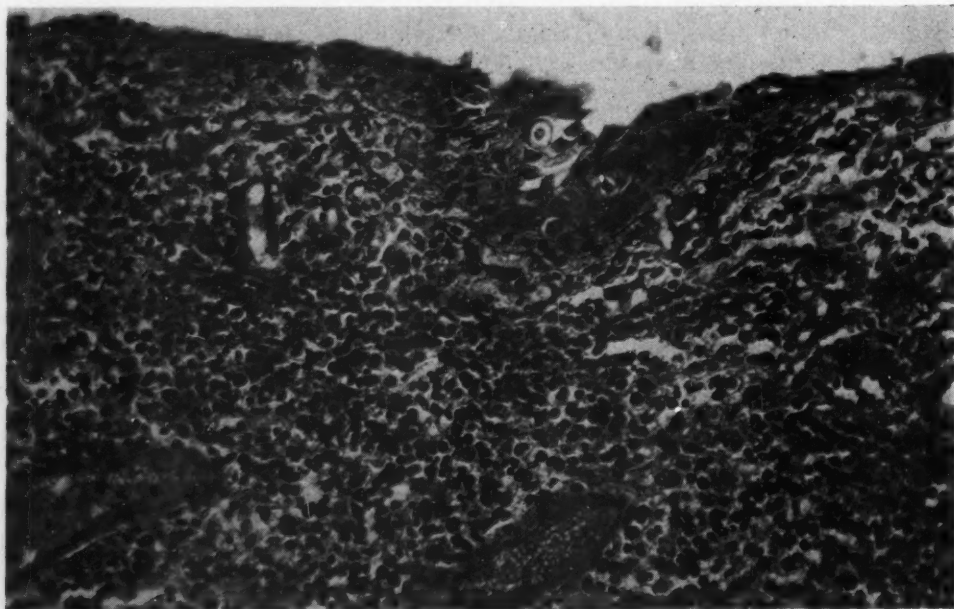


Fig. 2.—Cross section of the wall of the specimen showing a lining of transitional epithelium. ($\times 280$; reduced $\frac{1}{4}$.)

lumbar vertebra blood vessels entered the mass. The left ureter could be seen lying lateral and posterior to it, and a normal left kidney was visualized lateral to it. The right kidney was palpated and felt to be normal. The over-all length of the mass was 50 cm. (Fig. 1).

After the mass was removed, the bladder was filled with 200 c.c. of fluid to make certain there was no injury and was found to be intact. (This is a routine procedure we follow whenever there is any suspicion of possible damage to the bladder during surgery.) The posterior leaf of the left broad ligament and the posterior parietal peritoneum were then closed with continuous sutures. Penrose drains were placed extraperitoneally and another drain was placed into the peritoneal cavity. The abdomen was closed in layers, and a Foley catheter was left in the bladder.

The postoperative course was quite uneventful, although the patient was febrile for seven days. Management consisted of several blood transfusions, penicillin, streptomycin, and Chloromycetin. The peritoneal drain was removed on the third postoperative day and the extraperitoneal drains on the ninth postoperative day.

Bacteriologic report of the pus obtained from the mass revealed *Aerobacter aerogenes* and *Proteus vulgaris* infections. No tubercle bacilli could be found on smear or culture. The pathologic report stated that the specimen was lined by transitional epithelium and the pathologic diagnosis was a blind, accessory ureter (Fig. 2).

An intravenous pyelogram was done on the eleventh postoperative day and showed the left kidney and ureter displaced laterally, but otherwise normal; the right kidney and ureter were normal. A retrograde pyelogram done eight weeks after discharge from the hospital was normal.

The only information obtained from the hospital where the patient had been previously admitted was that she had been treated for vaginitis and pyelitis. A urine culture then revealed *Bacillus coli*.

Comment

In retrospect, the patient presented several clues to the true nature of her illness; she had psoas spasm, no adjacent pelvic induration, and no surrounding peritoneal reaction. These were overlooked, however, in the presence of the other gross findings and symptoms.

Te Linde³ mentioned that he had seen an acutely infected hydronephrotic ectopic kidney lying in the cul-de-sac and resembling a tuboovarian abscess, but no such extensive process as encountered here has been noted before. Whether the specimen represented only an accessory ureter or a ureter with a kidney which had been completely destroyed cannot be determined. It is quite possible that there was a third, rudimentary kidney, for Miller² stated that such kidneys are usually located above the normal left kidney. This would help explain why the mass extended so high.

Summary

A case of an infected accessory ureter or ureter and kidney, of unusual size and presenting as a pelvic tumor, is reported. The types of retroperitoneal tumors which may simulate the more common gynecologic tumors are given. When dealing with pelvic masses, gynecologists should keep these tumors in mind.

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LIPOMAS OF THE UTERUS

DIMITRY CHACHUTOW, M.D., AND ROBERT BRILL, M.D., PASSAIC, N. J.

(From Department of Laboratories, St. Mary's Hospital)

AT THE time of hysterectomy for leiomyofibroma, the tumor at times gives the impression of soft consistency. The gynecologic surgeon may then suspect sarcomatous alteration or ischemic degeneration or necrosis. If the specimen is incised, a yellowish, peculiar glistening appearance should suggest the rare possibility of a lipoma, as well as the infrequent but still far more common possibility of sarcoma. The diagnosis can be confirmed by frozen section.

Because of the paucity of published cases, and the excellent prognosis as compared to that of sarcoma, this case is being reported.

Decker⁴ in 1952 stated that during the period since 1857 there had been about 23 cases reported. Robertson and Gerber¹⁵ in 1953 reported a twenty-fourth case of lipoma. In recent publication, Brandfass and Everts-Suarez¹ reviewed the world literature and found that Lobstein in 1816 had recorded the first case of fatty tumor in the uterus, and Stroinski in 1880 had described for the first time a pure lipoma of the cervix.

Lipomas of the uterus, as the name implies, are tumors composed chiefly of fat cells although a small amount of accompanying fibrous tissue is present. The histogenesis of fatty tumors has been variously interpreted. This has led to considerable confusion and, as a result, these tumors have been designated as lipomas, lipomyomas, fatty tumors of the uterus, and lipomatosis of the stroma of the uterine fibromyoma.¹⁶ Although fat is not normally found in the uterus, lipomas can occur just as in the spleen, kidney, or brain, and most likely result from misplaced embryonic fat cells as Cohnheim⁷ suggested in 1882. Bruennings² favored the view that muscle cells are converted into fat cells. On the contrary, von Jacobsen⁹ attributed the development of the fat cells to the infiltration of the connective tissue cells with fat globules. Wilms¹⁸ explained their origin as displacement of embryonal rests along the Wolffian duct or its persistent remnant, the Gartner duct. Another theory was that fat cells proliferate into the uterus from the subserosal fat of the neighboring structures and also from perivascular fat cells accompanying the blood vessels into the uterus.^{12, 14}

Lipomas of the uterus occur in different forms. Ikonomou,⁸ in his publication on fat tissue tumors of the uterus, distinguished three categories: The first he named "pure lipomas." These tumors are composed of only fat cells. They are round and well encapsulated. The second group includes those with the addition of some fibromatous or myomatous tissue. Some authors call these tumors lipofibroma, lipofibromyoma or lipomyoma. To the third group, "immature lipomas," belongs liposarcoma of the uterus.

Petersen,¹¹ in his review of 50 cases of "mixed tumors of the uterus," reported 5 containing fat. These, however, were predominantly malignant tumors, except for those containing large numbers of fat cells, which seemed to be benign and were reported either following operation or as incidental findings at post-mortem examination.

The site of the reported lipomas is predominantly intramural, in the corpus, especially in the posterior wall, often just beneath the cornu.³ Review of the world literature,¹ however, with 9 cases occurring in the cornu and 6 in the lateral wall, discloses no predilection for any portion of the corpus. In size, the reviewed cases ranged from 1 cm. up to that of a human head.

Clinically, lipomas of the uterus have the same significance as fibromyomas. After operative removal, no metastases were observed.¹¹ Most tumors recorded were found in postmenopausal women.⁴ Brandfass and Everts-Suarez¹ in their review found that 67 per cent of lipomas occurred in women between the ages of 50 and 70, 11 per cent above 70, 11 per cent between 40 and 50, and 11 per cent under 40 years of age. Reich and Nechtow¹³ found one such tumor in a 30-year-old woman. The fact that lipomas are chiefly found in women after the menopause raises the thought that they may be related to the loss of ovarian function.³

Case Report

Mrs. D. E.,* 55 years old, was admitted to the hospital on Nov. 28, 1954. Her complaint was heaviness in the pelvis. She stated that she had suffered pelvic discomfort from time to time for the past two years. In the last three weeks, this symptom was aggravated and the patient was able to feel a "lump" in the abdomen. There was no history of abnormal uterine bleeding. Menstruation had always been regular, every 28 days and lasting 4 to 5 days. The menopause occurred at age 50. She had had three normal pregnancies and deliveries. The past history was essentially negative and the patient had never complained of any other distress.

Physical examination showed an obese patient with no abnormalities other than a large, hard, irregular, lobulated mass palpable in the lower abdomen and extending to the umbilicus. On vaginal examination the uterus appeared large, irregularly shaped, and freely movable. Urinalysis and serologic test for syphilis were negative. The hemogram also was within normal limits, although the hemoglobin of 14.6 Gm. and red cell count of 5 million per cubic millimeter suggested hemoconcentration.

At the time of operation the uterus was "about the size of a football" with a very large intramural tumor and a second similar subserous one on the fundus. The patient's postoperative recovery was uneventful.

Pathologic Examination.—*Gross:* The specimen consisted of a supracervically amputated uterus, measuring 8.5 cm. from fundus to internal os; 13 cm. across the fundus and 16 cm. in an anteroposterior direction. The enlargement was due to the presence of two ovoid, relatively soft tumors. The larger of these was located in the anterior fundal region; the second in the left broad ligament, widely separating the left Fallopian tube and ovary and markedly elongating the former. On section the large tumor mass was found to measure 14 cm. in diameter (Fig. 1) and to be composed of grayish tissue in lobular arrangement with areas that had a pale tan hue. The cut surface appeared somewhat more glistening than usual for a leiomyoma (Fig. 2). The mass in the left broad ligament measured 8 cm. in diameter and was similar in appearance (Fig. 1). A third 2 cm. sized nodule composed of gray-white fibers in whorled arrangement was also seen. The ovary measured 3 by 1.5 by 1 cm. and was not grossly remarkable. The separately received cervix was not remarkable.

*From the service of Dr. Frank Jani.



Fig. 1.



Fig. 2.

Fig. 1.—Cut surface showing both lipomas.

Fig. 2.—Close-up of cut surface showing the glistening appearance suggestive of sarcoma.

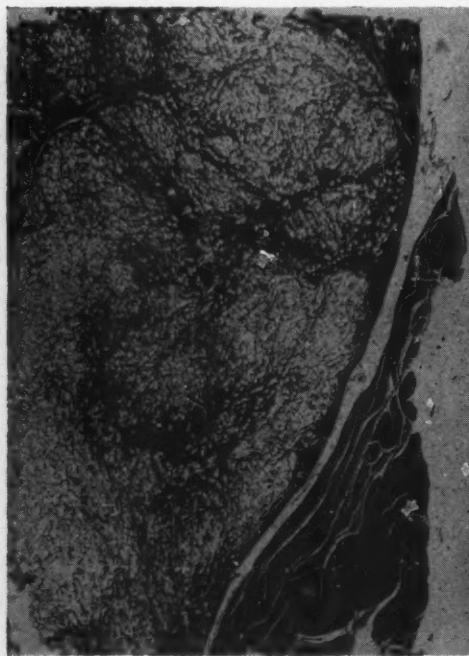


Fig. 3.

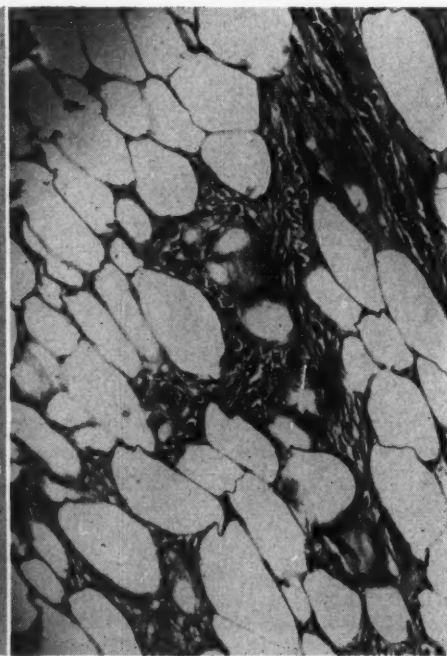


Fig. 4.

Fig. 3.—Photomicrograph of the encapsulated edge of one of the lipomas. ($\times 10$; reduced $\frac{1}{6}$.)

Fig. 4.—High-power view showing the histologically normal fat cells. ($\times 225$; reduced $\frac{1}{6}$.)

Microscopic: The small, 2 cm. sized nodule was composed of parallel smooth-muscle fibers in interlacing bundles. The other two larger lesions were composed of histologically normal fat tissue and variable amounts of collagenous tissue. In some areas only small amounts of fat were present but elsewhere large amounts were evident without inflammatory infiltrate to suggest that this is the result of inflammation and subsequent fatty change (Figs. 3 and 4).

Diagnosis: Lipomas of the uterus. Leiomyoma of the uterus. Chronic cervicitis. Fallopian tube and ovary.

Comment

On many gynecologic services, it is routine procedure to examine the surgical specimen before the peritoneal cavity is closed. If the case is one involving a uterine tumor, sections of the lesion may rarely present a glistening, pale yellowish appearance, rather than the usual gray-white fibers in whorled arrangement, so characteristic of leiomyofibroma. If this is interpreted as a sarcomatous lesion, the surgeon may spend additional time in lengthy exploration of the peritoneal and retroperitoneal tissues, searching for any evidence of metastasis. If, however, the possibility of lipoma is borne in mind, frozen section will confirm the diagnosis and the patient will be spared the additional anesthesia and surgical trauma.

Lipomas of the uterus are far less common than leiomyosarcomas. Herbert⁶ listed the incidence of the latter as between 0.39 and 2 per cent of uterine leiomyofibromas. On the other hand, lipomas are very uncommon, with only 34 cases recorded in the literature up to 1955.¹

Summary

1. A case of lipomas of the uterus is reported. This makes the thirty-fifth case since that first recorded in 1816.
2. Three distinct tumors were present: a small leiomyoma and two large lipomas.
3. In gross appearance, lipomas may be suggestive of leiomyosarcoma, but frozen section easily differentiates between these two.

We are indebted for the photomicrographs to Dr. E. O. Gilbert, Bureau of Pathology, Department of Health, State of New Jersey.

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Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Review of New Books

Colposcopy. By H. Hinselmann, with a Contribution on Colpophotography by A. Schmitt. Translated by W. R. Lang and J. Preyer. 38 pages with 39 figures. Wuppertal-Elberfeld, 1955, W. Girardet. \$4.50.

This brief monograph by the famous father of colposcopy includes sections on requirements for a colposcope and the manner in which a colposcopic examination should be performed. Following initial inspection of the cervix, the cervix is painted with acetic acid, salicylic acid, and Schiller's iodine solution. Colposcopic findings are described and atypical epithelia are classified. Professor Hinselmann rejects the diagnosis of carcinoma in situ and instead proposes a system of classification of atypical epithelia based upon colposcopic observation and proceeding from simple atypical epithelium to gross carcinoma. The section on colpophotography describes the technique of photography through the colposcope. There is a separate picture supplement to the book; it includes some very fine photographs taken through the colposcope.

After the diagnosis of atypical epithelium has been made, the atypical area is excised and studied microscopically. There is no question but that colposcopic examination will serve as a guide to proper biopsy of the cervix. Whether or not the method really justifies the beautiful studies of Dr. Hinselmann is another question.

A Handbook of Medical Hypnosis. By G. Ambrose and G. Newbold. 255 pages. London, 1956, Ballière, Tindall & Cox.

This introduction to medical hypnosis includes a discussion of historical and legal aspects involved. Of particular interest to the reviewer were two chapters devoted to obstetrics and one to gynecology. In these specialties there is an obvious relationship between psychological factors and physical symptoms. Skillful use of hypnosis in properly selected cases may well effect a more rapid and more lasting cure. Functional uterine bleeding, psychogenic amenorrhea, and functional dysmenorrhea are only a few conditions in which hypnosis can be used with success. By interesting case histories, the authors show the application of hypnosis to the management of labor and the antenatal period. A bibliography is presented at the conclusion of each chapter. The reviewer would like to caution the reader against considering hypnosis as a panacea instead of an effective diagnostic or therapeutic tool.

Konservative Therapie der Frauenkrankheiten. By H. A. Müller. Eighth edition. 425 pages. Wein, 1956, Springer-Verlag. \$7.60.

Conservative therapy in gynecology is the subject of this small book. It deals with menstruation and its disturbances, including those of the menopause; inflammations of the female genital tract; endometriosis; and tumors both benign and malignant. At times the author is reluctant to exchange indicated surgical therapy for the conservative approach. In spite of the fact that he has done an excellent job of bringing this edition

up to date in terms of modern therapy, he has not deleted outmoded and at times somewhat rather unphysiologic forms of therapy. The best example of this is the inclusion of the method of *Belastungstherapie*. The author states that this regimen is only occasionally used today in the treatment of exudates and parametrial masses. It consists of placing a 1 to 2 kg. shot-pouch on the abdomen and then, after positioning of the patient, filling the vagina with 0.5 kg. of mercury in a suitable bag. The mercury is supposed to fill the contours of the vagina and exert pressure. Over a period of time more mercury is added. This method is also advised for a fixed and retroverted uterus. Certainly because of the retention of old and probably regional therapy this book cannot be recommended to American physicians as a primary source of information.

The Premarital Consultation. By A. Stone and L. Levine. 90 pages. New York, 1956, Grune & Stratton. \$3.00.

Drs. Stone and Levine have written a volume full of good advice to physicians who give premarital consultations. They have included and elaborated on themes which their experience has shown to be significant. The section on genetics is quite up to date. The book contains an appendix which is concerned with the vaginal diaphragm as a contraceptive technique, marriage laws of various states, and birth control laws. The bibliography is helpful to doctors desirous of further information.

Roentgen Signs in Clinical Diagnosis. By I. Meschan. 1058 pages with 2216 illustrations. Philadelphia, 1956, W. B. Saunders Company. \$20.00.

This review is restricted to a consideration of Chapter 31, "Radiography in Obstetrics and Gynecology." This chapter is nicely subdivided into sections on determination of pregnancy; determination of multiple pregnancy; determination of fetal normalcy, age and development; determination of fetal viability or death; presentation of the fetus; study of the placenta; extrauterine pregnancy; cephalopelvic disproportion and pelvic measurements; and hysterosalpingography.

All sections are liberally illustrated with roentgenograms and other appropriate figures. The author describes only the method of pelvimetry used by himself, but makes the following pertinent comment, "It is important . . . to adopt that method of correction for magnification and distortion which is most feasible in his particular installation and to learn that method thoroughly. . . ." The author does not illustrate nor use some of the anteroposterior measurements of the midplane and outlet which are current and which are thought to be useful by obstetricians interested in x-ray pelvimetry. His attention to and discussion of pelvic architecture is satisfying.

The section on x-ray studies of the uterine cavity and the appendages is liberally illustrated. There is no attempt to present any methodology other than the author's.

Books Received

The following books have been received. Selected reviews will appear in later issues.

The Care of the Expectant Mother. By Josephine Barnes. 270 pages. New York, 1956, Philosophical Library. \$7.50.

The Clinical Management of Varicose Veins. By David W. Barrow. Second edition, 169 pages with 69 figures. New York, 1957, Hoeber-Harper. \$6.00.

Muscle Relaxants in Anesthesiology. By Francis F. Foldes. 210 pages. Springfield, Ill., 1957, Charles C Thomas, Publisher. \$5.50.

The Queen Charlotte's Text-Book of Obstetrics. By G. F. Gibberd, et al. Ninth edition. 547 pages with 246 illustrations. Boston, 1956, Little, Brown & Company.

Selected Abstracts*

The American Journal of Surgery

Volume 93, January, 1957.

*Schneider, P., and Dreizin, D. H.: Cervical Pregnancy, p. 27.

Schneider and Dreizin: Cervical Pregnancy, p. 27.

The authors present a case report of a cervicoisthmie pregnancy and discuss cervical pregnancy. They include a short review of the literature. The number of proved cervical pregnancies is 17. Differentiation is made between primary cervical implantation and that with placental attachment extending into the isthmus and corpus. The lack of decidua in the cervix enables the chorionic villi to be embedded in the wall of the cervix with subsequent rupture producing massive hemorrhage.

ROBERT C. KNAPP

The Canadian Medical Association Journal

Volume 75, No. 12, December 15, 1956.

Bowden, D. H., Goodfellow, A. M., and Snelling, C. E.: Observations on Neonatal Mortality, p. 1000.

Journal of Gerontology

Volume 11, October, 1956.

*Stoloff, I., Watkin, D. M., and Shock, N. W.: Age and the Ratio Tm P.A.H./Tm Diodrast in Man With a Note on the Self-Depression of Tm Diodrast, p. 388.

Stoloff, Watkin, and Shock: Age and the Ratio Tm P.A.H./Tm Diodrast in Man With a Note on the Self-Depression of Tm Diodrast, p. 388.

The glomerular filtration, effective renal plasma flow, and Tm (maximal tubular excretory capacity) were determined in two groups, one with the mean age of 40 years and the other of 79. The ratio of Tm PAH (para-aminohippuric acid) to Tm Diodrast was $2.45 \pm .06$ for the younger group and $2.45 \pm .16$ for the older group. Furthermore, the renal plasma flow using PAH or Diodrast was not significantly different. The authors felt that the transport mechanism for Diodrast by the renal tubule is able to re-establish itself even with a high plasma Diodrast concentration.

ROBERT C. KNAPP

The Lancet

Volume 2, September 8, 1956.

*Morris, N., Osborn, S. B., Wright, H. P., and Hart, A.: Effective Uterine Blood-Flow During Exercise in Normal and Preeclamptic Pregnancies, p. 481.

Morris, Osborn, Wright, and Hart: Effective Uterine Blood-Flow During Exercise in Normal and Preeclamptic Pregnancies, p. 481.

Using a method described previously (Morris, N., Osborn, S. B., and Wright, H. P.: *Lancet* 268: 323, 1955) the authors determined the clearance rates of radiosodium from

*Titles preceded by an asterisk are abstracted below.

uterine and thigh muscles before, during, and after exercise in 21 normal pregnant women and in 19 pregnant women who had hypertension believed to depend entirely upon the pregnancy. The mean diastolic blood pressure in the normal pregnant women rose from 73.3 before exercise to 85.5 during exercise and then fell to 75.8 after exercise. In the patients with pre-eclampsia these values were 93.3, 98.9, and 91.4. In pre-eclampsia, the mean uterine clearance rate of Na^{24} (the time required for the counting rate over the injection depot to fall to one-half of its initial value) was 7.17 before exercise, 8.75 during exercise, and 6.25 after exercise. The values in normal pregnant women were 4.07, 5.43, and 3.07. Similarly the leg clearance rates for Na^{24} were 14.15 (resting), 6.96 (during exercise), and 18.69 (after exercise) for normal pregnant women and 14.71, 7.85, and 15.00 for women with pre-eclampsia. Coincidentally, therefore, with the changes in blood pressure during exercise, there is an increase in blood flow through the legs and a diminution of blood flow through the uterus. In pre-eclampsia, the clearance rates that were obtained indicate that the blood flow through the uterus, which is already diminished in pre-eclampsia, decreases markedly during exercise.

The clinical observations that an active life is apt to be associated with a deterioration in the patient's condition in pre-eclampsia and that rest is likely to cause an improvement in the condition may have a rational basis. When the patient with eclampsia is at rest the blood pressure is reduced, the skeletal blood flow is reduced, and the uterine and splanchnic blood flow is increased, perhaps to a tolerable level.

DAVID M. KYDD

Volume 2, November 3, 1956.

*Smith, J. A. McC., Jennison, R. F., and Langley, F. A.: Perinatal Infection and Perinatal Death, p. 903.

Smith, Jennison, and Langley: Perinatal Infection and Perinatal Death, p. 903.

During the period April through June, 1955, two groups of women who were in labor or whose membranes had ruptured were studied. In Group I there were 137 women thought to have an intrapartum infection as manifested either by a maternal temperature of more than 98.6° F. or by a sustained fetal heart rate of 160 or more. Every alternate patient in Group I received 1.0 Gm. streptomycin twice daily and 500 mg. oxytetracycline every 6 hours (Group 1A). The remaining patients in Group I received no antibiotic drug (Group 1B). In Group II there were 99 women in whom no intrapartum infection was suspected. These women were used as controls and received no special therapy. There was no fetal mortality in Group II. In Group 1B, 10 babies died (14.7 per cent) and of these 5 had pneumonia. In Group 1A, 5 babies died (7.3 per cent) and there were no instances of pneumonia. Cultures were obtained from a high vaginal swab on admission of the patient and during the third stage of labor. In patients in Group II, 38 per cent of the first cultures and 32 per cent of the second cultures yielded a pathogenic organism (*Escherichia coli*, *Streptococcus faecalis*, nonhemolytic streptococci, and rarely a hemolytic streptococcus). In Group 1B, these values were 63 per cent and 30 per cent, and in Group 1A, 73 per cent and 50 per cent. Two per cent of the cultures of placental blood contained pathogenic organisms in Group II, 13 per cent in Group 1B, and 7 per cent in Group 1A. Because the organisms are of low virulence for the mother the signs are not conspicuous, but, when some degree of pyrexia is present or when the fetal heart rate rises above 160, treatment of the mother with an antibiotic for 48 hours before delivery appears to reduce fetal mortality. [The differences in percentages are not significant. *Editor*] In this connection the absence of fetal pneumonia in the treated Group 1A is stressed.

DAVID M. KYDD

Volume 2, December 1, 1956.

*Bisset, G. W., Lee, J., and Bromwich, A. F.: Oxytocic and Antidiuretic Activity in Blood From the Internal Jugular Vein in Man, p. 1129.

Bisset, Lee, and Bromwich: Oxytocic and Antidiuretic Activity in Blood From the Internal Jugular Vein in Man, p. 1129.

Blood was obtained from the jugular veins of 11 patients at the time they were undergoing major surgical procedures. Nine of these specimens of blood were tested for oxytocic activity by the method of Bisset and Walker (J. Physiol. 126: 588, 1954). In 2 instances no activity was detected; the mean concentration in the remaining specimens was 1.2 ± 0.26 m μ per milliliter (in terms of posterior pituitary lobe extract, PPLE). All the blood specimens were tested for antidiuretic activity by the method of Ames and Van Dyke (Endocrinology 50: 350, 1952). In only 4 of the specimens was activity found, and in these the concentrations in terms of PPLE ranged from 0.012 to 0.025 m μ per milliliter. Oxytocic activity was thus found in far higher concentration than antidiuretic activity and the suggestion is made that either the ratio of oxytocin to the antidiuretic hormone is high or that oxytocin is released independently of the antidiuretic hormone. Inasmuch as interfering substances having oxytocic activity such as potassium, 5-hydroxytryptamine, and pain-producing substance and other nonspecific factors have been eliminated in the method used and the fact that the activity is abolished by sodium thioglycollate, the presumptive evidence is that the activity is due to the hormones of the neurohypophysis.

It is suggested that the hormone oxytocin may influence the renal excretion of electrolytes in the male, possibly by causing a natriuresis. Possibly the functions of oxytocin and the antidiuretic hormone may be interrelated and the ratio of production of these hormones may be important.

DAVID M. KYDD

Volume 2, December 22, 1956.

*McNicol, M. W., and Hutchison, H. E.: Severe Toxic Reaction to Hydralazine, p. 1288.

McNicol and Hutchison: Severe Toxic Reaction to Hydralazine, p. 1288.

A 44-year-old patient who had steatorrhea and renal insufficiency developed severe hypertension. He was given 0.25 mg. Serpasil and 12.5 mg. Apresoline. After a week, the dose of the latter drug was doubled. After three weeks, his blood pressure was little changed and he developed diarrhea and trembling. Drugs were discontinued. He developed fever, anorexia, and lassitude, a hemorrhagic rash, and platelets disappeared from the blood smear. An anemia with severe depression of leukocytes occurred. After a month the patient gradually improved and the pancytopenia corrected itself. The general character of the illness suggested disseminated lupus erythematosus but no lupus erythematosus cells were found in two extensive searches. During the febrile phase of the illness the blood pressure fell to nearly normal limits.

DAVID M. KYDD

Volume 1, January 5, 1957.

*Wear, L. E.: Uterine Myoma as a Hereditary Disease, p. 25.

Wear: Uterine Myoma as a Hereditary Disease, p. 25.

Among the 15 female members of 3 generations of a family, there were 9 instances of uterine myoma. Because of this incidence in a family tree, the suggestion is made that the condition may be transmitted through males as well as females, and that this may explain the presence of myomas in daughters of women with no family history of this condition. The high incidence in this family suggests a dominant Mendelian inheritance.

DAVID M. KYDD

Volume 1, January 26, 1957.

*Preedy, J. R. K., and Aitken, E. H.: Plasma-Estrogen Levels in Late Pregnancy, in the Normal Menstruating Female, and in the Male, p. 191.

Preedy and Aitken: Plasma-Estrogen Levels in Late Pregnancy, in the Normal Menstruating Female, and in the Male, p. 191.

The concentrations of the estrogens in plasma were determined chemically by applying to plasma the method developed by Aitken and Preedy (Biochem. J. 62: 15, 1956) for the analysis of urine. The method involves a gradient elution partition chromatograph with subsequent fluorimetry.

In late pregnancy the ranges were: estrone, 2.65 to 10.3 mcg. per cent; estradiol-17 β , 1.25 to 2.93 mcg. per cent; and estriol, 4.28 to 17.5 mcg. per cent. In normal females in the luteal phase of the menstrual cycle, estrone varied from 0.215 to less than 0.06 mcg. per cent; estradiol-17 β was lower than 0.07 mcg. per cent; and estriol varied from 0.296 to less than 0.15 mcg. per cent. In normal males the levels were all very low, there being only one instance out of 5 in which any estrogen was measured (0.111 mcg. per cent of estrone). The method is specific and in pregnancy, at least, requires as little as 8 ml. of plasma. By using 18 ml. of plasma, concentrations as low as the following may be determined: estrone 0.06 mcg. per cent; estradiol-17 β 0.07 mcg. per cent; and estriol 0.15 mcg. per cent.

Although the urinary excretion of the three estrogens has been highest during the luteal phase of the menstrual cycle, only minute amounts could be detected in the plasma and no estradiol-17 β at all.

DAVID M. KYDD

Die Medizinische

Volume 1957, January 12, 1957.

*Döring, G. K.: The Diagnostic Value of the Basal Temperature in Gynecology and Obstetrics, p. 73.

Döring: The Diagnostic Value of the Basal Temperature in Gynecology and Obstetrics, p. 73.

The author considers that the correlation between rise in basal temperature and ovulation is well founded. He cites studies in which the temperature rise has been correlated with endometrial biopsy, vaginal smear, carbon dioxide tension in the lung, pregnanediol excretion, and observation of the ovaries at the time of laparotomy. He feels that one can distinguish an anovulatory cycle from an ovulatory cycle, even the onset of pregnancy and early disintegration of the corpus luteum. He reports that of 68 women who had intercourse once in the menstrual cycle, 67 became pregnant, having had relations within 6 days prior to the rise in basal temperature. One became pregnant on the ninth day preceding the rise in temperature (no explanation is offered).

FRANCIS B. O'BRIEN

Volume 1957, January 19, 1957.

*Sager, C. A.: The Early Recognition of Congenital Atresia of the Small Intestine, p. 108.

Sager: The Early Recognition of Congenital Atresia of the Small Intestine, p. 108.

The author reports the cases of 7 infants, term and premature, who were subjected to surgery of the small intestine because of early recognition of atresia. Four of the 7 survived. A high degree of suspicion should be aroused when there is vomiting in the first day of life, lack of a meconium stool, or hydramnios. If any of these criteria are present, the stomach should be sounded, a Farber test performed on the stool, and appropriate x-ray studies made.

FRANCIS B. O'BRIEN

Proceedings of the Society for Experimental Biology and Medicine*Volume 94, Number 1, January, 1957.*

*Johnson, J. F.: Changes in Plasma Prothrombin, Ac-Globulin, and Antithrombin Concentration Following Intravenous Administration of Estrogens, p. 92.

*Elliott, R. F., and Whitehill, A. R.: Placental and Mammary Transfer of Ingested Chlortetracycline in the Rat, p. 119.

Johnson: Changes in Plasma Prothrombin, Ac-Globulin, and Antithrombin Concentration Following Intravenous Administration of Estrogens, p. 92.

Twelve dogs were given 10 mg. of Premarin intravenously. Their prothrombin increased by about 40 per cent, with a maximum at about an hour after injection. The Ac-globulin showed a threefold increase, with a maximum at about two and one-half hours. Antithrombin decreased slightly. These changes were detectable at 15 minutes after injection and the values returned to control levels after three to four hours.

Theoretically, all of these changes tend to increase the coagulability of the blood.

LEON C. CHESLEY

Elliott and Whitehill: Placental and Mammary Transfer of Ingested Chlortetracycline in the Rat, p. 119.

In each of 3 groups, 10 pregnant rats 2 weeks from term were fed a standard diet containing, respectively, 0, 0.5, or 2.0 Gm. of chlortetracycline per kilogram of body weight. The rats were killed one day before the expected date of delivery. Analyses of the fetal tissue showed no chlortetracycline in the control series or in the series fed 0.5 Gm. per kilogram of the antibiotic. The fetuses from the rats fed 2 Gm. per kilogram contained an average of 0.36 (range 0.16 to 0.48) mcg. of chlortetracycline per gram.

In other experiments the rats were permitted to deliver and to nurse their young. Both the maternal mammary glands and the infant rat tissues were found to contain significant amounts of the antibiotic. In chronic feeding experiments, the fertility of female rats was somewhat increased.

LEON C. CHESLEY

Surgery, Gynecology and Obstetrics*Volume 102, May, 1956.*

*Davis, B. A., Latour, J. P. A., and Philpott, N. W.: Primary Carcinoma of the Ovary, p. 565.

Davis, Latour, and Philpott: Primary Carcinoma of the Ovary, p. 565.

Two hundred seventy cases of primary ovarian carcinoma seen at the Royal Victoria Hospital (1930-1954) are reviewed. More than 95 per cent of the cases were classified as either serous or pseudomucinous adenocarcinoma on microscopic examination. The over-all uncorrected five-year survival rate was 37.6 per cent in a 98.5 per cent follow-up. In a comparison of the results obtained with surgery alone and surgery plus radiation, no appreciable effect on prolonging life was found with the latter technique. The authors conclude, therefore, that x-ray is a valueless adjuvant to surgery in the treatment of primary carcinoma of the ovary.

VINCENT TRICOMI

Toko-Ginecologia Practica*Volume 1956, No. 146, November, 1956.*

*Rodriguez de Castro y Martinez, A.: Gastromelic Monster: A Case Without Precedent in the History of Medicine, p. 658.

Rodriguez de Castro y Martinez: Gastromelic Monster, p. 658.

A 23-year-old married woman who had had one normal child was admitted to the hospital after 296 days of amenorrhea. The antenatal course had been normal. She entered the hospital in active labor. The first stage lasted about one and one-half hours; the second, which lasted about five and one-half hours was terminated by the delivery of an abnormal 3,295 gram infant by means of manual assistance. The size of the child was normal, but he had two supernumerary extremities attached to the xiphisternum and an umbilical hernia. At operation 24 hours after delivery, the liver was noted to be enlarged with a segment of grossly normal large intestine attached. This intestine was not connected with the intestine of the host. The two supernumerary extremities were a distorted upper limb with an index finger and an abnormal lower limb with three toes. Except for a dilated right auricle and thickened entering veins and pericardium, other organs were relatively normal. The child succumbed after living about 50 hours.

FRANCIS B. O'BRIEN

Zeitschrift für Geburtshilfe und Gynäkologie

Volume 147, Number 1, September, 1956.

*Kleine, H. O.: Toxoplasmosis and Mongolian Idiocy, p. 13.

*Winter, G. F., and Pots, P.: Morphologic Examination of Changes of the Endometrium Induced by Drugs, p. 44.

*Bernroth, E.: The Menstrual Cycle and Cervical Secretions, p. 76.

*Hinz, W.: The Endometrium After Abortion, p. 82.

Kleine: Toxoplasmosis and Mongolian Idiocy, p. 13.

Three cases of Mongolian idiocy in babies of women with toxoplasmosis are reported. The author feels that this is a frequent etiology of the malformation, although other infections and noxious stimuli in the first trimester can also produce it. The previously held theory that Mongolism is hereditary is repudiated. The incidence of Mongolism can be reduced by advising women to avoid contact with animal species which are known hosts of *Toxoplasma histolytica*.

WALTER F. TAUBER

Winter and Pots: Morphologic Examination of Changes of the Endometrium Induced by Drugs, p. 44.

The endometria of 10 castrated patients and 25 with glandular hyperplasia were examined following treatment with progesterone caproate. The endometrium undergoes changes which resemble those of secretory endometrium, but the morphology is not identical with that of normal secretory endometrium. The author calls it rigid secretion (*starre Sekretion*). In several cases the dysfunctional bleeding of cystic hyperplasia was controlled by injection of estrogen and progesterone caproate.

WALTER F. TAUBER

Bernroth: The Menstrual Cycle and Cervical Secretions, p. 76.

Physical and chemical analysis of cervical mucus offers an easy nontraumatic method of evaluating endocrine changes in the menstrual cycle. This offers obvious advantages over laparotomy, culdoscopy, and curettage. At the time of ovulation the following characteristics are observed: tenfold increase in amount, increased transparency and ductility, and lower viscosity. Furthermore, there are cyclic changes (direction is not specified) in pH and osmotic pressure. Only 13 per cent of 600 patients studied were found to show a positive fern test. The cervical secretions of 90 per cent of 200 patients studied were indicative of sterility, and the remaining 10 per cent of cervical secretions were not indicative of sterility. This was considered to be due to break in technique. Further simple tests in sterility work-up are the Huhner test and its in vitro counterpart, the Kurzrok-Miller test.

WALTER F. TAUBER

Hinz: The Endometrium After Abortion, p. 82.

Changes in the endometrium after abortion lead to varied morphologic pictures. All embryonic components may be expelled, leaving only decidua to be recovered on curettage, just as in the presence of extrauterine pregnancy. Frequently a picture resembling cystic glandular hyperplasia is found. This is particularly true if there was no previous curettage or if the previous curettage was incomplete. At times, islands of hyperplasia are found within normal endometrium after regeneration of the mucosa. Such tissue frequently leads to subsequent menstrual irregularities.

WALTER F. TAUBER

Vol. 147, No. 2, October, 1956.

Noack, H.: Maternal Age and Obstetric Results, p. 204.

*Fink, A.: The Relation of Anomalies to Maternal Age, p. 214.

Lukas, K. H.: Psychogenic Disturbances in Gynecology, p. 231.

Schmid, H. H.: Autonomic Disturbances in Women, p. 238.

Fink: The Relation of Anomalies to Maternal Age, p. 214.

It is felt that oxygen lack is the immediate cause of congenital anomalies, whether the ultimate cause is virus disease, heredity, malnutrition, or radiation. The time of gestation during which the noxious influence is present determines the organ system affected. The particular danger of producing malformations with the use of x-rays for stimulation of ovarian function is emphasized. Central nervous system defects are found relatively frequently (38.4 per cent of malformations). Of all anomalies, only Mongolian idiocy shows a clear correlation with maternal age. Improved history taking, prenatal care, and follow-up may give a clearer picture of the etiology of malformations in the future.

WALTER F. TAUBER

Zentralblatt für Gynäkologie*Volume 78, September 22, 1956.*

*Mayer, A.: Comments on Myomectomy in Pregnancy, p. 1481.

Ebner, H., and Schneider, W.: On the Cytology of "Ascites Tumors" in Man, p. 1486.

*Schultze, K. W.: Induction of Labor by Massage of Connective Tissue, p. 1495.

Mosler, W.: Oxyhemoglobin in Serum From the Umbilical Cord, p. 1506.

Wille, P.: Active Thrombokinase in Amniotic Fluid, p. 1514.

Doehmann, H. J.: Bilateral Tubal Pregnancy of Varying Ages—A Case Report, p. 1523.

Mayer: Comments on Myomectomy in Pregnancy, p. 1481.

Pregnancy with fibromyomas of the uterus is occasionally complicated by severe pain which does not readily respond to analgesics. The pain is from pressure on adjacent organs, particularly on the bladder or rectum if the myoma is attached to the lower uterine segment or cervix, distention of the serosa, "mechanical peritonitis" caused by rubbing between subserous myoma and parietal peritoneum, red degeneration, or rotation of the uterus with embarrassment of venous drainage. Surgical treatment offers three possibilities: hysterectomy with the pregnancy in situ, therapeutic abortion, or myomectomy. The author rejects the first two approaches. Hysterectomy not only interrupts a pregnancy which may have followed a long sterility, but also precludes further pregnancy. Abortion, while relieving the pain, does nothing to remove the underlying pathologic condition.

In over 30 years, the author has performed myomectomies on 40 pregnant women. Single myomas were present in 75 per cent of the cases. The breakdown by period of gestation is as follows: 19 cases, first trimester; 9 cases, fourth month; 6 cases, fifth month; 5 cases, sixth month; and 1 case, seventh month. Abortion followed operation in 5 cases. In one case the operation was done as a last resort in threatened abortion. In another, the fetus was macerated. This gives a corrected abortion rate of 7.5 per cent. There were 3 operative deaths; 2 of these were from pulmonary emboli and the third from paralytic ileus following high doses of progesterone.

Technically it is advised to avoid Pfannenstiel incisions, obtain exposure by adequate abdominal incisions without displacing the uterus, and handle the uterus as little as possible and with gentleness. If the myoma lies posteriorly, it may be necessary to cut one round ligament and open the broad ligament on that side in order to achieve exposure. Hemorrhage has never presented a serious problem. Decreased likelihood of abortion is obtained by use of spinal anesthesia and progesterone in addition to careful surgical technique. Operation in early pregnancy is preferred because abortion is less likely to occur than premature labor.

Vaginal delivery ensued in 38 cases. Cesarean section was performed in one elderly primigravida and in one case of cephalopelvic disproportion.

WALTER F. TAUBER

Schultze: Induction of Labor by Massage of Connective Tissue, p. 1495.

In 68 of 108 cases in which the attempt was made, labor was induced by massage of the dermatomes with the same innervation as the uterus. Most of the refractory cases fell into two groups: one, those found not to be at term on later examination; the other, those in which there was uterine dysfunction when labor finally supervened. The author has found that connective tissue in the lumbosacral area becomes soft at term. When only patients with soft tissue were selected, labor was successfully induced in 14 out of 15 patients, and the remaining patient later went into inertial type of labor. Massage has been found to be most successful in the late afternoon and evening.

This method is recommended as safer than Pitocin induction and equally effective.

WALTER F. TAUBER

Volume 78, September 29, 1956.

*Geipel, K.: Primary Mortality in Radium Therapy of Gynecologic Carcinomas, p. 1538.

Riessbeck, K. H., and Geipel, K.: Clinical Experience With Radiation of Gynecologic Carcinomas, p. 1538.

Weber, E.: Criteria for Choosing the Vaginal Approach of Operation, p. 1556.

Sederl, J.: Closure of the Vault After Vaginal Hysterectomy, p. 1562.

Geipel: Primary Mortality in Radium Therapy of Gynecologic Carcinomas, p. 1538.

Primary mortality in radium therapy can be due to heart failure, pulmonary embolism, circulatory collapse, or bleeding. Pulmonary embolism can result from thrombosis near the site of radiation, and circulatory collapse from parasympathetic stimulation of radium therapy. Bleeding is an unlikely but theoretical possibility.

The author reports that of 650 patients treated there were 3 deaths from embolism, and these deaths were associated with early exertion. He advises that pretherapeutic cardiac evaluation and prophylactic treatment be as strict prior to radiation as to surgery.

WALTER F. TAUBER

Volume 78, October 6, 1956.

Adler, U., Koller, T., and Stamm, H.: Tuberculosis of the Female Genital Tract, p. 1569.

*Klees, E.: The Problem of Tuberculosis and Pregnancy in Relation to Pulmonary Resection, p. 1585.

*Hahn, J.: Results of Bacteriologic Study of Menstrual Blood in Tuberculosis of the Genital Tract, p. 1603.

Kremling, H.: On the Diagnosis of Tuberculosis of the Genital Tract, p. 1608.

*Kreiblich, H.: Does Isolated Tuberculosis of the Female Genital Tract Exist? p. 1611.

Podleschka, K.: Isolated Endometrial Tuberculosis, p. 1613.

Klees: The Problem of Tuberculosis and Pregnancy in Relation to Pulmonary Resection, p. 1585.

A review of the literature discloses the fact that in most cases of active pulmonary tuberculosis therapeutic abortion leads to worse results than those achieved by letting the pregnancy go to term. Forty-seven cases collected from the world's literature show that normal pregnancy after pulmonary resection is possible with no deleterious effects on the patient.

From his own service the author reports 4 cases of pregnancy following pneumonectomy and one following segmental resection. Three patients had normal vaginal deliveries; 2 had abortions by vaginal hysterotomy because of active tuberculosis in the remaining lung tissue. One of these patients was much worse after the pregnancy had been interrupted.

WALTER F. TAUBER

Hahn: Results of Bacteriologic Study of Menstrual Blood in Tuberculosis of the Genital Tract, p. 1603.

A study was made at Lübeck City Hospital of 327 patients with tuberculous pelvic inflammatory disease discovered since 1944. Diagnosis was first made through the following methods: laparotomy (with definitive surgery), 139 cases; curettage, 74; biopsy, 1; cul-de-sac aspiration: histologic examination, 2, bacteriologic examination, 8; bacteriologic examination of menstrual blood, 98; and autopsy, 5. Between the years 1947 and early 1956, 1,775 bacteriologic examinations were done on the menstrual blood of 233 patients. Positive results (336) were obtained on 174 patients (75 per cent). These included 70 positive cultures and 321 positive guinea pigs. Fifty-five specimens were positive by both methods. After a third repetition, 89.7 per cent of the cases were positive. Only 2 per cent became positive after a seventh attempt. Positive results were obtained during subsequent study of the menstrual blood of 64 per cent of 141 patients in whom the diagnosis had previously been made by surgical means. This percentage is considered good because intensive chemotherapy was already in progress at the time of the bacteriologic study. Of the 78 patients in whom the diagnosis was established at the hospital by the menstrual-blood method, 32 had no prior history of tuberculosis in other organs. Bovine tuberculosis was found in only about 5 per cent of the cases.

The chief advantage of using menstrual blood in the diagnosis of tuberculosis is the fact that the method is completely innocuous. The chief disadvantage is the long time required, i.e., 6 to 8 weeks.

WALTER F. TAUBER

Kreiblich: Does Isolated Tuberculosis of the Female Genital Tract Exist? p. 1611.

From 1930 to 1953, 6,583 autopsies were performed on females at the author's hospital. Of these, 610 had tuberculosis, including 54 with genital tuberculosis. In only one of these was genital tuberculosis an isolated finding. The author warns therefore that radical gynecologic surgery should be undertaken for tuberculosis only after careful evaluation, and vigorous medical and supportive therapy is indispensable in all cases.

WALTER F. TAUBER

Item

American Board of Obstetrics and Gynecology

Applications for certification (American Board of Obstetrics and Gynecology), new and reopened, for the 1958 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is Sept. 1, 1957. No applications can be accepted after that date.

Candidates for admission to the Examinations are required to submit with their application a typewritten list of all patients admitted to the hospitals where they practice for the year preceding their application or the year prior to their request for reopening of their application. This information is to be attested to by the Record Librarian of the hospital or hospitals where the patients are admitted and submitted on paper 8½ by 11 inches. Necessary detail to be contained in the list of admissions is outlined in the Bulletin and must be followed closely.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

ROBERT L. FAULKNER, M.D., Secretary
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EDITORS

HOWARD C. TAYLOR, JR., and WILLIAM J. DIECKMANN

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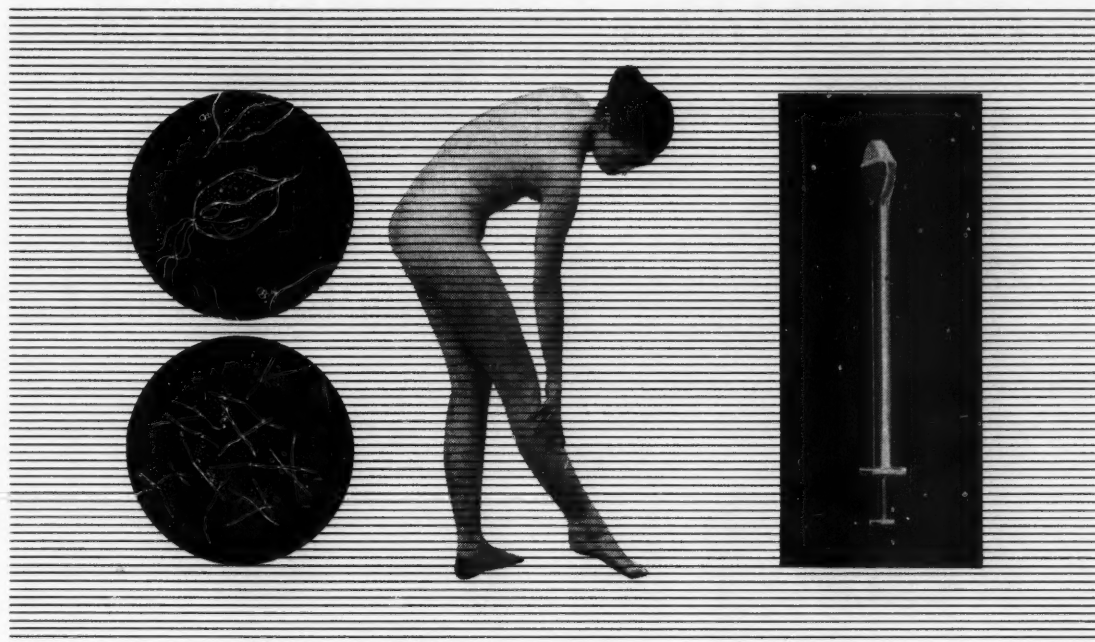
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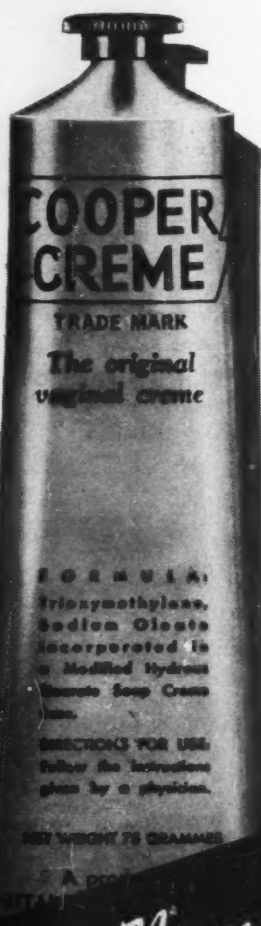
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References:

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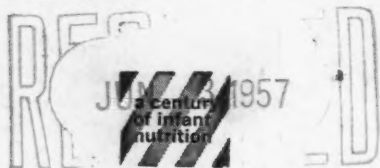
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